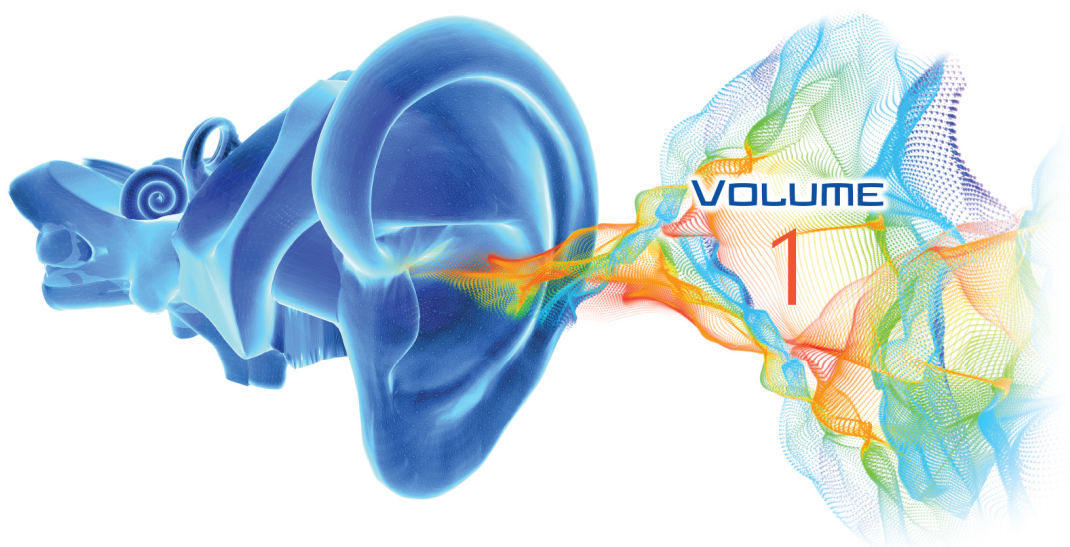


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**ERNO LARIVAARA
AND
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PREFACE

This 4 volume set presents important research on audiology and hearing. Some of the topics discussed herein include:

- cochlear implantation
- chronic tinnitus
- the auditory brainstem response
- sensorineural hearing loss
- autoimmune inner ear disease
- presbyastasis

VOLUME 1

Chapter 1

INNER EAR ENDOTHELIAL DYSFUNCTION DUE TO OXIDATIVE STRESS: A POSSIBLE ROLE IN THE PATHOGENESIS OF SENSORINEURAL HEARING LOSS

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Francesco Maldotti and Chiara Bianchini***

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ABSTRACT

Over the past years, researchers have identified reactive oxygen species (ROS) as major factors mediating sensorineural hearing loss (SNHL). SNHL is caused by loss of cochlear hair cells or neurons and this damage is irreversible. SNHL is a common disorder as it is reported to affect millions of people, of any age, around the world; SNHL also has different presentations, from mild to profound, including low and high frequencies patterns.

ROS can damage inner ear directly by injuring cellular DNA or indirectly by inducing apoptosis of the inner ear sensory cells (hair cells or spiral ganglion neurons). Recent observations also link oxidative stress to further damage in the inner ear by causing endothelial dysfunction in the cochlear microcirculation. Since the role of endothelial cells in microcirculation is crucial as they control and regulate the local blood flow (i.e., through the expression of several adhesion molecules), their injury can induce relevant damages to cochlear hair cells or spiral ganglion neurons. The cochlea, in fact, is particularly vulnerable to hypoxic or ischaemic damage as: (i) it is provided with a terminal capillary bed and it is not supplied by collateral vessels which could restore blood flow in ischaemic regions; (ii) cochlear hair cells have a high metabolic activity. Understanding the aetiopathogenetic mechanisms of SNHL is crucial also in order to identify possible innovative therapeutic approaches.

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INTRODUCTION

Deafness is one of the most prevalent disabilities in our society, and there is a considerable social and economic demand for the development of new therapeutic approaches for hearing loss. Also, it is well known that the loss of hair cells within the human inner ear results in hearing disorders that significantly impair quality of life [1].

The mammalian cochlea is unable to replace lost hair cells (inner and outer) and this is the cause of an irreversible hearing impairment. Hair cell loss may result from several conditions such as aging, exposure to noise, infectious diseases and use of ototoxic drugs such as cisplatin and aminoglycosides [2, 3, 4]. Several studies show that oxidative stress can play a relevant role in the pathogenesis and development of inner ear diseases [2, 3, 4, 5]; oxidative stress can directly mediate metabolic cellular damages in the inner ear sensory cells, but it has recently been proposed that it may also cause further damage by inducing endothelial dysfunction in inner ear microcirculation [6, 7, 8].

Understanding the inner ear mechanisms of damage and, therefore, protecting the inner ear from irreversible degeneration represent a primary objective, since, up until now, there are no therapeutic options for sensorineural hearing loss except for hearing aids and cochlear implants [1].

ENDOTHELIAL DYSFUNCTION AND INNER EAR

There is rising evidence that endothelium is at major risk of ROS-induced lesions and that this damage is most evident in microcirculation. A damage to endothelial cells, and in particular of those of the cochlear microcirculation, can be relevant as they actively participate to the control and the regulation of the microcirculation at several levels, such as a) maintaining blood in a fluid state; b) regulating the exchange of fluid and macromolecules between blood and tissues, at capillary level; c) regulating local blood flow and local immuno-surveillance [8, 9, 10-18].

It has been reported that high concentrations of circulating ROS (especially hydrogen peroxide, H₂O₂) may induce apoptosis or sudden death of endothelial cells. In “in vitro” models of oxidative stress, it has been shown that high amounts of H₂O₂ can cause endothelial cells apoptosis or, at highest doses, sudden death of cultured endothelial cells [9, 19].

The failure of endothelial cells to perform their activities, as it can result from endothelial cells apoptosis / death, can be therefore defined as endothelial dysfunction [8].

Experimental Data

Only few experimental data about endothelial dysfunction and pathogenesis of inner ear disease, mostly guinea pigs and rats, are currently available. Guo et al. described inner ear histopathological changes possibly related to endothelial dysfunction [20]. They detected hair cell loss (mainly at the cochlear basal turn), thickening of vascular intima, and stenosis of the cochlear arteries of apolipoprotein E gene deficient mice, in which impairment of endothelial

function is caused by increased production of superoxide radical (O_2^-) and reduced endothelial NO synthase activity [20]. In a guinea pig model, Selivanova et al. also reported a reduced expression of Vascular Endothelial Growth Factor, a mitogen for endothelial cells that specifically promotes angiogenesis and vascular permeability of endothelial cells, due to intense noise exposure (70 db SPL / 1 hour), in all cell types of the organ of Corti, including those of the stria vascularis [21]. Noise induced hearing loss has been associated with alterations in cochlear blood flow, and also Picciotti et al. suggest a role for VEGF in the regulation of the vascular network in guinea pigs inner ear after acoustic trauma and during auditory recovery [22].

Syka et al. also showed that mice treated with statins present larger amplitudes of distortion product otoacoustic emissions than non-treated control group, indicating a better survival/function of outer hair cells. The decreased expression of intercellular and vascular adhesion molecules in the aortic wall and the reduced endothelial inflammatory effects may therefore influence positively the inner ear blood supply [23].

In addition, Gloddle et al., advanced the hypothesis that microvascular inner ear disease could be related to EC damages, as disrupted ECs promote the onset of a local vasculitis by secreting proinflammatory cytokines like IL-1, IL-6 or TNF- α in addition to expressing of adhesion molecules, in a guinea pig model [24]. Microvascular stenosis with consequent inner ear ischemic damages could result from the persistence of these immunopathological mechanisms, in experimental conditions [24].

Clinical Evidences

In humans, ROS appeared to be involved in hair cell damage in some cases of hearing loss (i.e., Menière syndrome). Moreover, recent literature reports link endothelial dysfunction to some inner ear diseases such as sudden sensorineural hearing loss, tinnitus and presbycusis.

Sudden Sensorineural Hearing Loss (SSNHL). Quaranta et al. and Haubner et al. investigated the role of endothelial dysfunction in the inner ear, indicating that as increased expression of circulating adhesion molecules (VCAM-1) in patients affected by sudden sensorineural hearing loss, could be linked to endothelial dysfunction and micro-vascular impairment in SSNHL [6, 7].

Tinnitus. Neri et al. observed that oxidative stress markers (such as malondialdehyde, 4-hydroxynonenal, glutathione peroxidase, nitric oxide, L-ornitine, thrombomodulin and von Willebrand factor) are increased and nitric oxide production reduced in brain circulation reflux blood of patients with acute tinnitus. These oxidative stress conditions could be able to cause a general cerebro-vascular endothelial dysfunction, and therefore also a inner ear microcirculation dysfunction for the Authors [25].

Presbycusis. Studies of the aging cochlea showed a decrease of antioxidant defences such as glutathione level in the auditory nerve or antioxidant enzymes in the organ of Corti (hair cells) and spiral ganglion neurons. Significant loss of hair cells and spiral ganglion neurons, as well as a systematic degeneration of endothelial cells of the stria vascularis, has been experimentally observed in mice lacking superoxide dismutase [26-29].

Unilateral vestibular syndrome (AVS). Labyrinth microvascular abnormalities have been hypothesized in AVS patients. Speculating that skin microcirculation may mirror vascular function in other body districts, Rossi et al. have demonstrated that AVS patients present skin

endothelial dysfunction using endothelial-dependent vasodilator acetylcholine (ACh) and endothelial-independent vasodilator sodium nitroprusside (SNP), and this can be linked to a more probable ischemic origin of AVS [30].

CONCLUSION

It is already well known that oxidative stress, due to an increase activity of reactive oxygen species (ROS) and consequent damage of intracellular biochemical processes, represents an important factor in the pathophysiology of several types of inner ear disease (i.e., sudden sensorineural hearing loss, acoustic trauma). However, recent evidence also suggests that, in some situations oxidative stress could cause further damage by inducing endothelial dysfunction within inner ear microcirculation. Unfortunately, so far, the involvement of endothelial dysfunction in the pathogenesis of inner ear disease is supported by few and weak evidences available on animal models, and clinical evidences are also inconsistent. Further studies will be then necessary in order to understand the possible pathophysiological mechanisms involved in endothelial dysfunction within inner ear microcirculation [8].

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Chapter 2

HEARING SCREENING FOR SCHOOL CHILDREN

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ABSTRACT

Hearing screening is an integral component in virtually all school health screening programs. It has long been recognized that hearing loss will have negative consequences on children's communication abilities and educational performance unless early identification and management is arranged. School-based screening allows for the detection of children with hearing loss who have not been identified at an earlier stage (for example, in a newborn hearing screening program) and for children who have developed hearing loss after early childhood (for example, children with a progressive, inherited hearing disorder). This chapter provides an overview of pure-tone audiometry, the standard method for hearing screening in school children, and details the main established guidelines for screen protocols. Other hearing and ear health methods have also been considered for school-based programs, such as tympanometry, otoacoustic emission recording, and teacher/parent questionnaires. These procedures are discussed and their advantages and limitations outlined. Conventional hearing screening programs are not effective in detecting children with high tone, noise-induced hearing loss or children with auditory processing difficulties. Potential alternative screening protocols to identify children with such problems are presented. Advances in technology may alter the practice of hearing screening in the future. For example, telehealth-based screening may serve a useful role in future programs and genetic screening for hearing disorders may enhance the early detection of some cases of hearing loss.

DEVELOPMENT OF SCHOOL HEARING SCREENING

Children with sensory disorders have been of particular concern to school health screening services from their foundation.

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Permanent childhood hearing loss may have a serious long-term impact on the communication abilities, educational achievement, socioeconomic status, and overall quality of life of an individual, as well as generating major financial costs for the community as a whole (Access Economics, 2006). School health services recognized that the early identification and management of hearing loss could mitigate the associated level of disability. Henderson (1975, p. 15) cites the Chief Medical Officer's 1908 report to the British Board of Education which stated that: "It is not usually practical during the routine examination of large numbers of children to test accurately the exact condition of the hearing capacity of a child ... [but] it is important that a careful examination should be made of all children in whom there is any reason to suspect defective hearing." By 1911, the Chief Medical Officer had revised this guidance and considered a hearing test should be given to "every child who is old enough to respond." A whispered voice test for school children was introduced in the United Kingdom in the 1920s, although its inadequacies were acknowledged (Henderson, 1975) and more scientific methods of hearing screening were introduced in the 1930s. By the 1940s pure-tone audiometry screening was a standard test throughout the country (Stevens and Parker, 2009). Australian school medical services incorporated a rudimentary hearing assessment component from the early 1900s (Skurr, 1978) and, in the United States, formal school hearing health examinations also developed as early as 1924 (McFarlan, 1927). Wall and Bühner (1987) noted that, by 1943, twenty American states had laws requiring school screening for hearing loss. With economic advancement, hearing screening was initiated in many other regions. For example, in Hong Kong audiometric screening for children in government primary (elementary) schools commenced in 1968 and became universal by 1981 (Lam et al., 2006). Screening audiometry has now come to be considered an established and essential aspect of school health practice throughout the developed world, and in many developing countries (McPherson and Olusanya, 2008).

School screening audiometry has concentrated on the detection of possible hearing disorders in elementary grade school children. This is appropriate because it is advantageous to arrange the earliest possible treatment or habilitation for hearing loss and because many cases of previously undetected hearing loss are noted at the time of school entry (Roeser and Northern, 1981). From the viewpoint of educators, intervention should be as early as possible so that it does not negatively affect academic performance.

In many countries, universal newborn hearing screening programs have now been established and the early detection of congenital hearing loss is common (Leigh, Schmulian-Taljaard, and Poulakis, 2010). However, the hearing screening of school children can be justified by the prevalence of hearing loss that is not detected by universal newborn hearing screening, due to factors such as delayed onset hearing loss or acquired hearing loss. British data suggests that the prevalence of bilateral, permanent hearing impairment increases by at least 50% (and perhaps up to 90%) between the newborn period and the ages of 9-16 years (Fortnum, Summerfield, Marshall, Davis, and Bamford, 2001).

In addition, there are limitations to newborn screening technology that mean it may not detect cases of mild hearing loss (Leigh, Schmulian-Taljaard, and Poulakis, 2010) and newborn screening programs may have a high non-compliance rate for follow-up (Danhauer, Pecile, Johnson, Mixon, and Sharp, 2008), leading to some children remaining unidentified until school entry. Approximately 3% of school age children in developed countries may have hearing loss in one or both ears (Marttila, 1986; Mehra, Eavey, and Keamy, 2009; Parving, 1999).

GOALS OF SCHOOL HEARING SCREENING

Screening programs need clear goals to be effective (Lescouflair, 1975). The two most influential sets of professional guidelines for hearing screening, both within and outside of North America, are those issued by the American Association for Speech, Language, and Hearing (ASHA) and the American Academy of Audiology (AAA). The broad ASHA (1997) goal for hearing screening is to identify children likely to have hearing impairment that may interfere with education, health, development, or communication and this aim is widely adopted in school programs. The AAA guidelines (2011) are similarly concerned with the identification of hearing loss that affects perception of speech and, hence, development of language-based skills. In both guidelines, it is implicitly or explicitly stated that this goal includes detection of children with unilateral as well as bilateral hearing loss.

PURE TONE SCREENING AUDIOMETRY

Nearly all school hearing health programs make use of pure tone screening audiometry as the fundamental component of their procedures (see Figure 4.1). This is for a number of reasons. Pure tone diagnostic audiometry is the gold standard for assessment of hearing loss. This involves measurement of perceived threshold intensities for a series of standard tones that cover the range of sounds required for optimal detection of speech.

It is convenient to base screening on the same procedure, using a pass/fail criterion intensity instead of determining threshold and to use a restricted range of test tones (test frequencies) that are critical for speech perception.

In addition, the sensitivity and specificity of pure tone screening audiometry has always been found to be better than that of any rival technique (Berg, Papri, Ferdous, Khan, and Durkin, 2006; Sideris and Glatke, 2006). FitzZaland and Zink (1984) noted sensitivity and specificity of 93% and 99%, respectively, in a well-conducted screening program.

Essentially, tones at fixed, single frequencies are presented at fixed intensity levels and the child is instructed to respond to a perceived signal by raising a hand, pressing a response button, or in some other standard manner. Earphones are the sound source and generally a practice tone is first presented to the child at a level clearly above the test tones (often at 40 or 60 dB HL) to introduce the child to the type of sound to be used. Test sounds are then presented first to one ear and later the other ear, and the presence or absence of a behavioral response from the child is recorded for each tone. No attempt is made to find the hearing threshold for a tone if the child does not respond at a particular frequency (Roeser and Northern, 1981).

Since the goal of screening is to detect hearing loss that may adversely affect speech perception, the test frequencies and intensities chosen should reflect this aim. ASHA guidelines (1997, p. 41) call for screening at 20 dB HL “in the frequency region most important for speech recognition”. Generally, this frequency region is considered to be from 500 Hz to 4000 Hz. However, ambient noise conditions in schools are rarely optimal for hearing screening (Choi and McPherson, 2005; Knight, Nelson, Whitelaw, and Feth, 2002; Shield, Greenland, and Dockrell, 2010) and low frequency ambient noise will often mask quiet test tones at 500 Hz, leading to high false-positive rates (McPherson, Law, and Wong, 2010).

The current ASHA guidelines recognize this constraint and recommend testing at 1000 Hz, 2000 Hz, and 4000 Hz only. The AAA (2011) guidelines make identical recommendations. A recent European consensus statement on hearing screening (Skarzynski and Piotrowska, 2012), while not making specific suggestions for test frequencies, states that hearing loss greater than 20 dB HL may have adverse effects on the development of communication skills, cognitive development, and academic achievement—in effect endorsing the ASHA and AAA recommendations for screening intensity level. It should be noted that many school screening agencies set their own criterion intensities and frequencies and these may not reflect standard guidelines (Meinke and Dice, 2007). However, any criterion set should be evidence-based (Wong and Hickson, 2012) and rigorously justified.

Pass/fail criteria may vary a great deal in pure-tone screening audiometry programs. Wall, Naples, Buhner, and Capodanno (1985), in a large survey of American professionals involved in school screening, found that failure to detect a signal at two frequencies was deemed a test failure for about one-third of respondents, others used one frequency, more than two frequencies, two consecutive frequencies, or a pure-tone average greater than a pre-determined level as a criterion for ‘failure’. Both ASHA and AAA guidelines define failure as a lack of response at any frequency in either ear.

The two guidelines differ somewhat in how ‘failure’ is determined. AAA (2011, p. 45) guidelines recommend “presenting a tone at least twice but no more than four times” if a child fails to respond. ASHA (1997) guidelines call for reinstruction, repositioning of earphones, and same day rescreening for any child who fails to respond at any frequency. Screening audiometers can be purchased specifically for this task.

These instruments provide a restricted test frequency range, usually from 500 Hz to 4000 Hz, and also limit earphone output intensity levels.



Figure 4.1. School screening using pure tone audiometry.

PERIODICITY OF SCREENING

Ideally, it would be advantageous to screen all elementary school children for hearing and middle ear disorders on an annual basis. However, the associated practicalities rarely allow for this (Roeser and Clark, 2004). Guidelines tend to prioritize the screening of younger grades and/or high-risk populations, defined by Roeser and Clark (2004, p. 118) as those cases that are: new to a school, repeating a grade, commencing speech-language therapy, returning to school following serious illness, delayed in development, displaying emotional or behavioral problems, involved in noisy coursework, or are absent during previous routine screening. To assist in the decision-making regarding which particular grades to screen, AAA (2011) provided a summary of findings from an unpublished analysis of hearing screening results from three school districts in Colorado and Florida, US.

Notably, it was found that approximately 90% of new hearing losses were detected by screening in preschool, kindergarten, and grades 1, 2, and 3. This rate increased to up to 97% if including grade 5 or 6 also.

Alternatively, ASHA's (1997) guidelines specify annual screening of all children from kindergarten through to grade 3, as well as in grades 7 and 11. Furthermore, children should be screened as needed, requested, or mandated. ASHA is also a proponent of screening of high-risk cases as described above, with the addition of the factors of: concern from parent/caregiver, health care provider, teacher, or other school personnel; family history of late or delayed onset hereditary hearing loss; recurrent or persistent otitis media with effusion (OME) for at least three months; craniofacial anomalies, including those with morphological abnormalities of the pinna and ear canal; stigmata or other findings associated with a syndrome known to include sensorineural and/or conductive hearing loss; head trauma with loss of consciousness; and, reported exposure to potentially damaging noise levels or ototoxic drugs.

Program managers should carefully consider the time of year when hearing screening is held. It is preferable to avoid times of the year that are known to be peak seasons for colds and influenza or for environment-related allergies (Richburg, Davie, and Smiley, 2012) since these are times of higher student absence rates and higher prevalence of transient conductive hearing loss.

PROGRAM MANAGEMENT

Hearing screening in the school environment may be performed by a variety of personnel, including, but not limited to: audiologists, audiometrists, speech-language pathologists, audiology assistants, school nurses, psychologists and specialist educators, and health workers. Personnel choices may be dictated by state licensure requirements or by district/program managers. Richburg and Imhoff (2008) noted that when hearing screening programs were supervised by an educational audiologist, testing protocols were more uniform than when non-audiologists were in management positions. The World Health Organization (2001) reported significant variation in the screening results obtained by minimally trained, junior testers in comparison with experienced testers (with $\geq$ one year's experience in audiometry).

Further, Northern and Downs (2002) noted that inexperienced testers, by incorrectly placing headphones, can create a threshold shift of up to 35 dB HL.

They may also provide unsuitable instructions, provide verbal and physical cues, and use inappropriate stimulus presentation length. In recognition of such studies and of the fact that many school districts in the US use screening programs that are managed by personnel other than audiologists, AAA (2011) recommended that school hearing screening programs at least utilize a single or small group of local audiologists in an advisory capacity.

The audiologist(s) could provide valuable input regarding higher administrative functions of the program, such as choice of screening technology and protocols, training and monitoring of testers, equipment maintenance and calibration, and follow-up pathways and procedures (Roeser and Clark, 2004).

ASHA's (1997) guidelines clearly specified that performance of hearing and/or middle ear screening of children aged 0-18 years should be limited to clinically certified audiologists and speech-language pathologists, or support personnel under the direct supervision of a certified audiologist.

Test Environment

In order to minimize the false-positive rate, it is crucial that testing is performed in an environment with low ambient noise (Roeser and Clark, 2004). For instance, the school room selected for testing should be located away from high noise sources such as cafeterias, music rooms, air-conditioners and other mechanical equipment, high-volume road traffic, and high-volume pedestrian traffic as often occurs near offices and toilet facilities.

Alternatively, the use of mobile test vans and booths could be considered if finances allow. This is particularly important if wanting to ensure that under-identification does not occur for cases of unilateral and minimal/mild bilateral hearing loss (White and Munoz, 2008). Roeser and Clarke (2004) recommend against the routine use of noise-excluding headsets, in view of placement effects, unless utilized by experienced testers.

These authors also remind us of the importance of performing simple biological checks to assess whether background noise levels are appropriate (i.e., establishing hearing thresholds at least 10 dB below the screening level at all test frequencies for a person with known normal hearing, AAA, 2011) or, if possible, directly measuring noise levels using a sound level meter against ANSI standards (1999).

The maximum allowable noise levels for pure tone screening in accordance with ASHA (1997) protocols are: 49.5 dB SPL at 1000 Hz, 54.5 dB SPL at 2000 Hz, and 62 dB SPL at 4000 Hz. For AAA (2011) protocols, these are 50, 58, and 76 dB SPL at 1000, 2000, and 4000 Hz, respectively. Finally, testing should occur in environments with minimal visual distractions that could impact upon the child's concentration and contribute to elevated false-positive rates.

Accountability and Other Concerns

The program supervisor, preferably an audiologist, should assume responsibility for the screening system's accountability, risk management, and program evaluation (see AAA, 2011, and ASHA, 1997, for full details).

Accountability refers to adherence to confidentiality and consent requirements, maintenance of the system database, referral tracking, and counseling. Risk management requires the audiologist to evaluate risk factors associated with the screening program and to develop procedures to minimize or eliminate those factors (e.g., consideration of infection control, calibration of equipment, quality assurance procedures, and system errors at all levels).

Program evaluation to ascertain the effectiveness of a screening system is discussed in Chapter 1.

ALTERNATIVE SCREENING METHODS

As noted by Meinke (2011), school-based hearing screening has become synonymous with pure tone screening. Despite multiple, promising technological advances since the inception of school screening in the 1920's, very little has changed and the hearing screening landscape is still characterized by standard pure tone testing with a widespread lack of standardization between programs (Bamford et al., 2007; Meinke, 2011). It is certainly time for the everyday practice of school hearing screening to benefit from the type of rigorous research, systematic evaluation, and in-depth attention that has been typically afforded to universal newborn hearing screening programs worldwide. Presented below are some alternative screening methods that could be considered for inclusion in the modern school hearing screening test battery, followed by discussion of follow-up management pathways, and mention of some potential future directions in this field.

Tympanometry

Tympanometry is used in the assessment of middle ear function; it is not a test of hearing but, rather, a test of the mechanical properties of the tympanic membrane and other middle ear structures. The middle ear system is an essential component of the auditory pathway, conducting sound from the outer to the inner ear. Disruption of middle ear function can produce a conductive hearing loss that can be temporary, fluctuating, or permanent in nature.

Tympanometry is a minimally invasive, quick, painless, and objective test that involves placement of a small, disposable probe tip into the entrance of the external auditory canal in order to create an hermetic seal (refer to Figure 4.2).

As the air pressure within the canal is varied from +200 to -400 daPa, the volume of the canal alters accordingly due to movement of the middle ear. A tympanogram is produced; a graph of the admittance (compliance or mobility) of the middle ear system against pressure. When air is present in the middle ear cavity, the tympanogram will display a peak pressure that corresponds with the air pressure within the middle ear space (Roush, 2001).

Measurement parameters obtained typically include equivalent ear canal volume (Vea), peak compensated static acoustic admittance (Ytm), tympanometric peak pressure (TPP), and tympanometric width (TW).

The shape of the tympanogram, along with the associated values, is judged either against the classification system developed by Jerger (1970), against specific normative criteria, or against professional practice guidelines.

Under Jerger's system, a "type A" tympanogram is associated with normal middle ear compliance and pressure (usually indicative of normal middle ear function), a "type B" tympanogram is associated with no changes in compliance with changes in pressure (suggestive of middle ear pathology such as OME or tympanic membrane perforation if accompanied by an abnormally large ear canal volume), and a "type C" tympanogram is associated with normal compliance in the presence of excessively negative pressure (as is seen in Eustachian tube dysfunction). Refer to Figure 4.3 for display of these typical tympanogram shapes seen in school children.

In regard to the use of specific normative criteria, these may take into consideration the age, gender, ear, or even racial heritage of the child (e.g., Li, Bu, and Driscoll, 2006). Finally, tympanometric screening results for school children may be analyzed in accordance with professional practice guidelines, such as those produced by AAA (2011), whereby a "failed" screen would be indicated by a TW of ≥ 250 daPa (the preferred criteria), or Ytm of < 0.2 mmhos, or TPP of -200 to -400 daPa (although this criterion alone should not trigger a medical referral).

As previously mentioned, although not a direct test of hearing status, tympanometry can be a useful addition to the audiological battery, as 49-66% of children with a type B tympanogram will have at least a mild degree of conductive hearing loss, compared with only 2-13% with other tympanometric profiles (National Health and Medical Research Council, NHMRC, 2002). For children aged 4-6 years, FitzZaland and Zink (1984) reported type B or C tympanograms to have a sensitivity ranging from 91.2 – 92.7% and a specificity ranging from 91.1 – 97.8% in the detection of hearing loss. These values increased to 100% and 97%, respectively, when tympanometry (type B tympanogram or Type C with ≤ -200 daPa) was used in conjunction with pure tone screening.



Figure 4.2. Tympanometry screening at a rural elementary school near Nanjing, Jiangsu province, People's Republic of China.

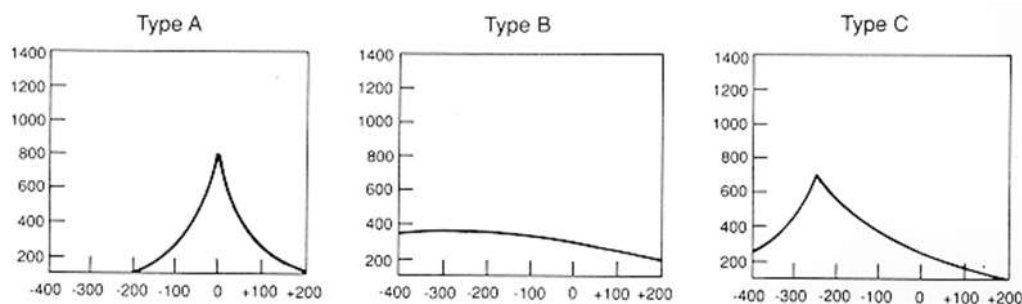


Figure 4.3. Typical tympanogram shapes observed during school screenings, using Jerger's (1970) classification system.

Furthermore, tympanometry demonstrates high sensitivity and specificity in the detection of OME when measured against a gold standard of myringotomy or pneumatic otoscopy (New Zealand Health Technology Assessment, 1998). In particular, type A tympanograms have a very high sensitivity in ruling out the presence of OME, and type B tympanograms have a sensitivity of 78-90% and a specificity of 63-94% in ruling in the presence of OME. These latter rates alter to 100% and 75%, respectively, if combined with type C tympanograms (New Zealand Health Technology Assessment, 1998).

Whilst there is little doubt concerning the appropriateness of tympanometry in detection of OME, support for its application in school-based screening programs is less conclusive. A suitable rationale for its inclusion might be if (a) OME was found to definitively cause long-lasting adverse effects upon a child's development and (b) that such effects could be averted by intervention (New Zealand Health Technology Assessment, 1998). However, the evidence to support these assumptions is conflicting and although a short-term correlation between OME and development has been recognized, a precise causal relationship has not. Adding to the uncertainty is the very nature of OME in childhood; it is a fluctuating disease subject also to seasonal variation, thus, single screening points throughout time are unlikely to detect all affected children. Furthermore, the rate of spontaneous resolution of OME is known to be high (Tos, 1984; Williamson, Dunleavy, Baine, and Robinson, 1994). Consequently, several professional bodies currently recommend against the routine, first-line use of tympanometry in school hearing screening programs (e.g., NHMRC, 2002; AAA, 2011).

It is suspected that the effects of OME on child development appear to be mediated by the associated hearing loss, although the exact degree and duration of loss needed to produce the negative sequelae remain unclear (AAA, 2011). In addition, of children with OME, 30-40% will experience recurrent episodes and 5-10% will experience episodes lasting in excess of one year (Tos, 1984; Williamson et al., 1994). Should the middle ear effusion be present for longer than three months, recovery is unlikely to occur in the absence of medical intervention (Tos, 1984; Williamson et al., 1994). Further, pure tone screening alone is not overly sensitive to middle ear disorders (Roeser and Clark, 2004). For these reasons, combined with the recognition of the noisy environments in which all school children must listen and learn and in which those with any degree or type of hearing loss can be considerably disadvantaged, some programs choose to include tympanometry in their basic test battery that is administered to all children. Others choose to apply tympanometry in the testing of those at high-risk of OME as per the AAA Position Statement on Identification of Hearing Loss and Middle Ear Dysfunction in Preschool and School-Age Children (1997).

Still others recommend its use as a follow-up or rescreening method. For instance, the AAA Childhood Hearing Screening Guidelines (2011, p. 46) state that tympanometry should be employed as an immediate next stage screening and/or a second stage screening for those who have failed pure tone or otoacoustic emission screening.

Tympanometry results should assist in clarifying the nature of the failure and in promoting the most efficient management pathway. Furthermore, AAA proposes that tympanometry could be considered as a first line screening tool for children in preschools, kindergartens, and grade 1 in situations where medical professionals and the school systems jointly decide to target OME in addition to cases with hearing loss.

The AAA guidelines also provide test protocol recommendations for tympanometry. Importantly, the tympanometer should be calibrated on a daily basis in accordance with manufacturer instruction. (A lightweight, easily portable device with a 226 Hz probe tone should be selected.) Prior to test commencement, visual inspection of the outer/middle ear using otoscopy should occur, in order to check for conditions that may necessitate medical referral or prohibit testing (e.g., tympanic membrane perforation, foreign bodies, blood in the ear canal, excessive cerumen, active discharge, etc.). Test results should be interpreted in accordance with the previously described criteria. Exceptions to these criteria include children with ventilation tubes who may be passed in the presence of a type B tympanogram with large Ve, and children of Asian heritage who may be passed with Ytm values of <0.2 .

Otoacoustic Emissions

Otoacoustic emissions (OAEs) may be defined as low-intensity, acoustic energy produced by the cochlea and recorded in the ear canal (Probst, Lonsbury-Martin, and Martin, 1991). Originally described by Kemp (1978), such emissions are believed to reflect energy leakage that is radiated out by the cochlea as a result of its outer hair cells actively processing and amplifying incoming low-intensity sound. One particular class of OAEs occurs as a result of deliberate acoustic stimulation; evoked OAEs, which include both transient evoked OAEs (TEOAEs) and distortion product OAEs (DPOAEs). TEOAEs are so named as the emissions are commonly elicited by brief acoustic stimuli, such as Gaussian-shaped broadband clicks or tone bursts. Presentation of the stimulus results in a clear, frequency-dispersive response or “echo” detected in the ear canal within a short, time-locked window. The nomenclature of DPOAEs reflects the stimulus being a pair of pure tones that interact in the cochlea to produce a third tone (the distortion product).

To complete this electrophysiological test, the screener must place a small probe (comprised of a transducer and microphone/receiver) into the entrance of the ear canal, to create an acoustic seal. The adequacy of the probe fit is then assessed via visual analysis of the waveform display. Automatic stimulus presentation is followed by automatic amplification, filtering, and digitization of the response, after which the software can provide a programmed pass/fail judgment based on the OAEs signal-to-noise ratio (SNR) and other so desired measurement parameters, such as reproducibility (for TEOAEs, see Figure 4.4) or amplitude (for DPOAEs, see Figure 4.5). Refer to Roush (2001) for further details of the OAE test method.

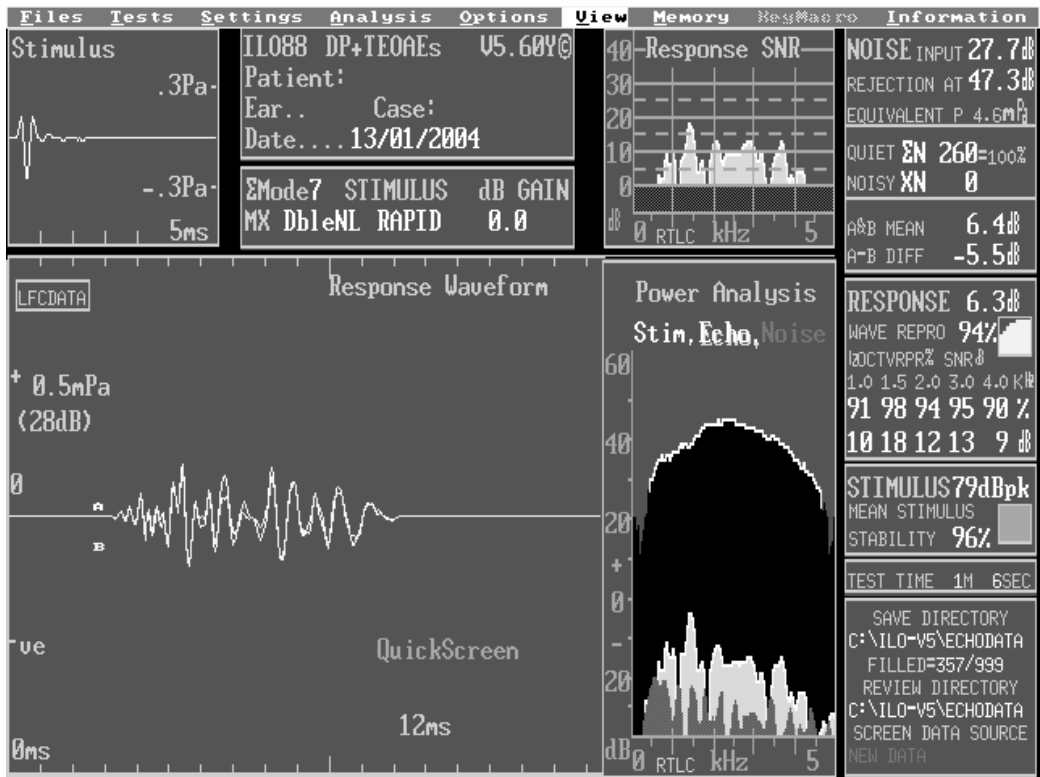
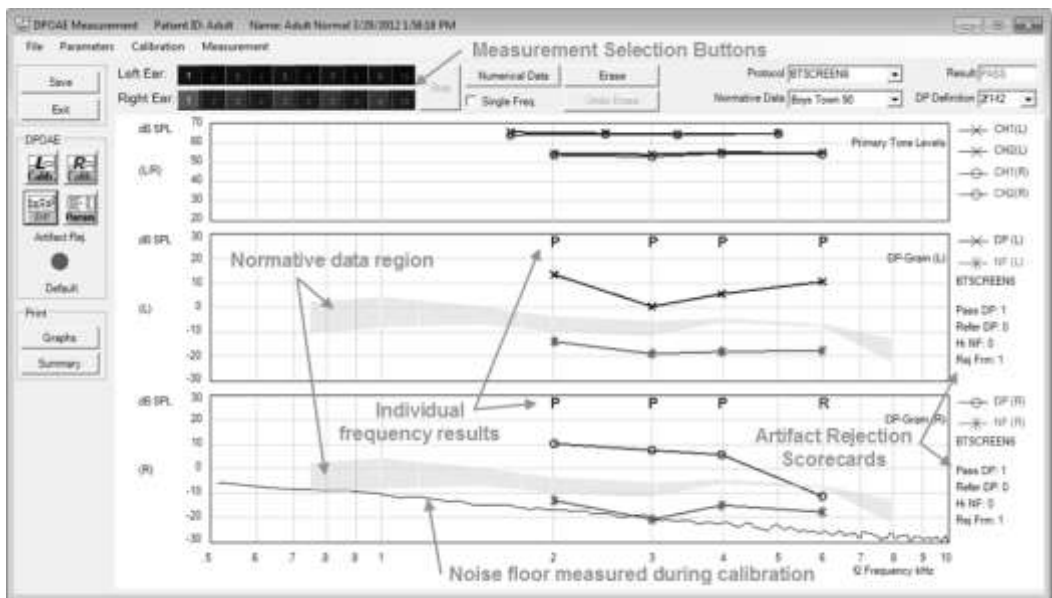


Figure 4.4. An example of the TEOAE test screen (taken using an Otodynamics ILO88 system).



Source: Taken using a Starkey DP2000 system, image courtesy of Starkey Laboratories.

Figure 4.5. An example of the DPOAE test screen. (Note: “DP” refers to the amplitude of the distortion product emission, and “NF” refers to the noise floor.)



Figure 4.6. School-based screening using Otoacoustic Emissions testing.

Typically, TEOAEs can be detected in persons with normal hearing sensitivity and otological status. DPOAEs can be detected in those with less than a moderate degree of hearing loss (i.e., normal hearing or a mild loss). Although neither are tests of hearing per se, they are often used to suggest or confirm the presence of hearing loss. Their presence is usually interpreted as indicative of normal cochlear (inner ear) function, whilst their absence can suggest outer hair cell damage and, hence, hearing loss. However, it is worth keeping in mind that failure of OAE testing is also associated with a plethora of potential influences including middle ear dysfunction (e.g., OME), instrumental factors (e.g., inappropriate stimulus characteristics), and environmental factors (e.g., high levels of ambient noise).

In summary, passing of an OAE test is suggestive of normal audiological function up to the level of the cochlea; however, failure merely indicates increased risk of the presence of a conductive or sensory hearing loss and/or middle ear pathology.

Both tests carry the advantages of being simple in test administration, non-invasive, objective, and resilient in non-sound treated settings. The duration of testing is also remarkably short, at less than a minute, assuming low noise levels. For these reasons, OAEs have been employed extensively in universal newborn hearing screening programs across the world. Researchers are now interested in their application in the screening of older children, such as in elementary schools, as a potential replacement for the traditional pure tone test (see Figure 4.6). However, professional guidelines, including those of ASHA (1997), AAA (2011), and NHMRC (2002), have yet to endorse their routine use in this context, due to the inferior sensitivity and specificity of OAEs, as well as an extensive need for further research.

What is known to date concerning TEOAE screening in school-aged populations is that:

- The test is highly feasible for mass screening in elementary schools (AAA, 2011; Driscoll, Kei, and McPherson, 2001; Georgalas, Xenellis, Davilis, Tzangaroulakis, and Ferekidis, 2008; Nozza, Sabo, and Mandel, 1997; Taylor and Brooks, 2000);

- Sensitivity has been shown to range between 0.65-1.0, depending on the gold standard of choice (AAA, 2011; Driscoll et al., 2001; Georgalas et al., 2008; Nozza et al., 1997; Sabo, Winston, and Macias, 2000);
- Specificity has been shown to range between 0.8-0.969 (AAA, 2011; Driscoll et al., 2001; Nozza et al., 1997; Sabo et al., 2000; Sliwa, Hatzopoulos, Kochanek, Senderski, and Skarzynski, 2011; Taylor and Brooks, 2000);
- Negative predictive values tend to be high, for example, 0.98, whilst positive predictive values are typically low, for example, 0.25 (Driscoll et al., 2001; Georgalas et al., 2008);
- Accuracy and efficiency indices are also typically high, for example, up to 0.88 and 0.91, respectively (Driscoll et al., 2001);
- Combining tympanometry with TEOAE testing does not lead to improved sensitivity and specificity (AAA, 2011; Driscoll et al., 2001; Georgalas et al., 2008; Nozza et al., 1997);
- TEOAEs cannot predict middle ear status and, thus, cannot replace otoscopy or tympanometry (AAA, 2011; Driscoll et al., 2001; Georgalas et al., 2008; Nozza et al., 1997);
- Choice of pass/fail criteria is paramount to achieving adequate test performance, with criteria used for neonates not necessarily transferrable to older children (AAA, 2011; Driscoll et al., 2001);
- Failure rates can range up to 21%, dependent upon the pass/fail criteria selected among other factors (Driscoll et al., 2001; Sabo et al., 2000);
- Normal emissions may be recorded in children with mild hearing losses (20-30 dB HL) (AAA, 2011);
- Testing is unlikely to be able to be completed for low-frequency stimuli (e.g., <1000 Hz or <2000 Hz), even in sound-treated environments, due to physiological and ambient noise levels (AAA, 2011; McPherson and Olusanya, 2008);
- Low-frequency pass/fail criteria have not been established to date (AAA, 2011); and
- The test does not assess beyond the outer hair cells of the cochlea and, thus, cannot detect children with auditory neuropathy/dys-synchrony (AN/AD) whereby outer hair cell function is normal but neural transmission in the auditory pathway is impaired producing a neural hearing loss (AAA, 2011; Rance, 2005).

Regarding DPOAEs in school-based screening programs, it has been found that:

- The test is highly feasible for mass screening in elementary schools (Lyons, Kei, and Driscoll, 2004);
- Sensitivity and specificity have been shown to approximate 0.7 and 0.9, respectively, if excluding low frequencies such as 1.1 kHz (Lyons et al., 2004);
- Negative predictive values have been reported as high, for example, 0.94, whilst positive predictive values appear moderately high, for example, 0.76 (Lyons et al., 2004);
- A high efficiency index has also been reported, for example, 0.87-0.91 (Lyons et al., 2004);
- Combining tympanometry with DPOAE testing does not lead to improved sensitivity and specificity (Lyons et al., 2004);

- DPOAEs cannot predict middle ear status and, thus, cannot replace a screening battery comprised of both pure tone testing and tympanometry (AAA, 2011; Lyons et al., 2004);
- Choice of pass/fail criteria (SNR cut-offs) is frequency dependent (AAA, 2011; Lyons et al., 2004);
- Failure rates range up to 18% and may be reduced further by incorporating two-stage screening protocols, however, loss to follow-up then becomes a concern (AAA, 2011);
- Normal emissions may be recorded in children with mild hearing losses (up to 40 dB HL) (McPherson and Olusanya, 2008);
- Testing is unlikely to be able to be completed for low-frequency stimuli (e.g., <1000 Hz), even in sound-treated environments, due to physiological noise levels (AAA, 2011; McPherson and Olusanya, 2008);
- Low-frequency pass/fail criteria have not been established to date (AAA, 2011); and
- As per the TEOAE test, testing cannot detect children with AN/AD (AAA, 2011; Rance, 2005).

Based upon these findings, it is clear that further research is necessary before OAEs can be accepted as a replacement for the typical pure tone screening test. In particular, AAA (2011) noted that test and equipment parameters require additional investigation, along with blinded test performance studies, the establishment of developmental norms and associated pass/fail criteria, training protocols, cost analyses, noise reduction schemes, and, potentially, the development of technology that would mitigate the effects of abnormal middle ear function upon the recorded emissions.

Nonetheless, AAA (2011) concluded that the use of OAEs combined with reflectance measures of middle ear status may result in improved screening practices in the future.

Questionnaires

Although an obviously cost effective method, with the added benefit of raising awareness of childhood hearing loss and its consequences (McPherson and Olusanya, 2008), the use of questionnaires to detect children at risk of hearing loss and/or other otologic pathologies is limited by their dependency on third party observation and motivation (Newton, Macharia, Mugwe, Ototo, and Kan, 2001). Other limitations of the questionnaire method include its known weakness in detecting cases with milder degrees of hearing loss and unilateral impairments (Newton et al., 2001). In addition, although parental concern is an important risk factor for sensorineural hearing loss in children, the sensitivity and specificity of parental concern are low even in the presence of severe or profound hearing loss (NHMRC, 2002). Furthermore, at least 50% of children who develop a postnatal hearing loss do not display any notable risk factors (Kennedy, Kimm, Cafarelli Dees, Campbell, and Thornton, 1998; Mehl and Thomson, 2002), upon which questionnaires are usually based. In general, questionnaires, as a sole method, have not been viewed as suitable for hearing screening purposes.

Despite the common perception, several studies have shown questionnaires to possess some potential in school-based hearing screening applications (Hind, Aitkins, Haggard, Brady, and Grinham, 1999; Li, Driscoll, and Culbert, 2009; Newton et al., 2001). For

instance, Li and colleagues (2009) examined the test performance of a questionnaire designed specifically for the screening of rural Chinese school children (the revised Chinese Hearing Questionnaire for School Children; CHQS-II).

This questionnaire, completed by parents/caregivers, consisted of an 11-item, Yes/No checklist constructed by the researchers to detect children at risk of otitis media with effusion (OME) and/or at least a moderate hearing loss in one or both ears. Analysis showed the CHQS-II to be moderately accurate (.62) as a screening system when compared with the gold standard diagnostic test battery of otoscopy, tympanometry, and pure tone audiometry. Its sensitivity, or ability to detect those at risk of hearing loss or middle ear infection, was also moderate (.67). However, its overall efficiency was poor (.56). In essence, there was a high likelihood that a passing child would not have a hearing loss/middle ear disease but only a low likelihood that a failing child would actually have an otologic problem. As the CHQS-II test performances indices did not approximate those of conventional screening techniques, its immediate use was not recommended. A very similar pattern of findings was observed in a hearing questionnaire study of Brazilian preschoolers by Gomes and Lichtig (2005).

It appears that the potential of questionnaires in the hearing screening of school children may lie not so much in their use as an alternative to traditional methods but, perhaps, as an adjunct. In particular, questionnaires may provide valuable information concerning auditory status and history that is not otherwise easily obtained. For example, questionnaires could prompt parents/caregivers to ask their children about the occurrence of tinnitus and exposure to noise. Similarly, they may be used to collect risk factor data, such as: a family history of late-onset hearing loss; otitis media with effusion for at least three months; craniofacial anomalies; stigmata associated with syndromes including hearing loss; head trauma with loss of consciousness; ototoxic drug use; and parent/teacher/health care provider concern regarding hearing, speech, language, or learning abilities (ASHA, 1997).

Modifications to Traditional Pure Tone Screening

Liao, Lien, and Young (2010) commented on the limitations of traditional pure tone screening in school-aged children; notably that pure tone screening typically produces pass/fail results only, providing little information concerning exact hearing status. This does not allow for easy and accurate comparison of repeat or monitoring screenings, of the like that may be performed for cases of otitis media or noise-induced hearing loss. In addition, a simple “fail” result can lead to distrust from parents and teachers, who may be wary of false positives associated with school hearing screenings, leading to a lack of cooperation with management recommendations.

Thus, Liao and colleagues devised the Hearing Scale Test (HST), a modified pure tone screening method, based on the concept of the Landolt C vision-test chart. The HST utilizes 10 hearing scales from S_1 to S_{10} , with each scale containing four frequencies (0.5, 1, 2, and 4 kHz) and separated by 5 dB HL (range = 0 – 45 dB HL). Minimum audible hearing scales (the stimulus level at which the child responds correctly at all four test frequencies) are determined using a computerized, semi-automated audiometer. Scales S_1 to S_5 are equivalent to a typical pure tone screening “pass,” whilst S_6 to S_{10} are comparable with a pure tone “fail.” The procedure was trialed on 384 third-graders in a Taiwanese elementary school, taking approximately 2-3 minutes per child to complete. No significant difference (and a high

level of agreement) was observed between the results of the HST and the results of traditional pure tone screening methods. Further analysis showed that the HST results could be interpreted as follows: S_1 to S_5 are indicative of normal hearing, S_6 and S_7 are suggestive of possible hearing loss, and S_8 to S_{10} or no response are symptomatic of confirmed hearing loss. With further widespread trials, the HST could be a successful alternative to the standard pure tone screen.

Other modifications to the traditional pure tone technique include the use of video testing (Bento, Albernaz, Di Francesco, Wiikmann, Frizzarini, and Castilho, 2003), whereby the four frequency sequence generated by an audiometer has been digitally recorded onto a video/CD. The disk can then be played in any test location that has access to a VCR or CD player. Bento et al. (2003) applied this method to 122 first-grade school children in Brazil and reported 100% sensitivity and 79.8% specificity when compared with pure tone audiometry. Although not capable of detecting unilateral hearing impairment, the researchers noted that such a modified technique may be useful for school screening in regions where standard test equipment and suitably qualified staff are not readily available.

With the increasing viability of computer-based audiometry, computerized screening audiometry methods deserve consideration. In the majority of school screening situations the screener is not an audiologist and a procedure that was based on an automatic test algorithm could enhance the quality of testing and reduce personnel training time and costs.

A recent pilot study of one commercially available audiometer software package found a good relationship between conventional hearing screening and computer-based screening in a group of 80 elementary school children (McPherson, Law, and Wong, 2010).

Finally, costs associated with false-positive cases could be reduced by development of noise-cancelling earphones for school screening purposes. Noise-cancelling technology is now commonly used in headphones (Schumacher, Kruger, Jeub, Vary, and Beaugeant, 2011). Lo (2012) reported, in a study of 232 elementary school students, that significantly fewer referrals were made in a screening program when noise-cancelling headphones were used compared to conventional audiometric earphones.

Other Methods

Alternatives for the hearing screening of school children such as acoustic reflex testing and the use of speech stimuli tests are currently not supported due to unacceptably high false-positive and high false-negative rates, respectively (AAA, 2011; NHMRC, 2002).

Furthermore, non-calibrated stimuli (e.g., the whisper test) should not be used in any capacity (ASHA, 1997).

FOLLOW-UP ACTIONS

A two-stage screening program is recommended by AAA (2011), in view of variables such as earphone placement, child behavior, and fluctuating/transient pathologies. By definition, AAA suggests that the two-stage protocol should include a same-day retest of failed

cases, followed by a rescreening performed after a designated period of weeks (see Figure 4.7 for an example of a two-tiered program pathway).

For suspected cases of middle ear pathology, ASHA's (1997) guidelines recommend this period to be 6-8 weeks; AAA state a minimum of 8 and a maximum of 10 weeks.

As noted by AAA, there is a trend for lower failure and referral rates with increased periods between screenings. However, for suspected cases of permanent hearing loss, it would be wise to minimize delays in diagnostic assessment and, therefore, it would be wholly appropriate to refer immediately following same-day rescreen (refer to AAA, 2011, for full details of rescreening recommendations).

In the event that referral to a medical practitioner is required for investigation of suspected middle ear pathology, AAA (2011, p. 50) suggests that the screener should include, if known, information concerning the duration and laterality of pathology, all test results from each test occasion, evidence/concern regarding speech and language abilities, and additional conditions that may exacerbate the effects of middle ear pathology in the referred case.

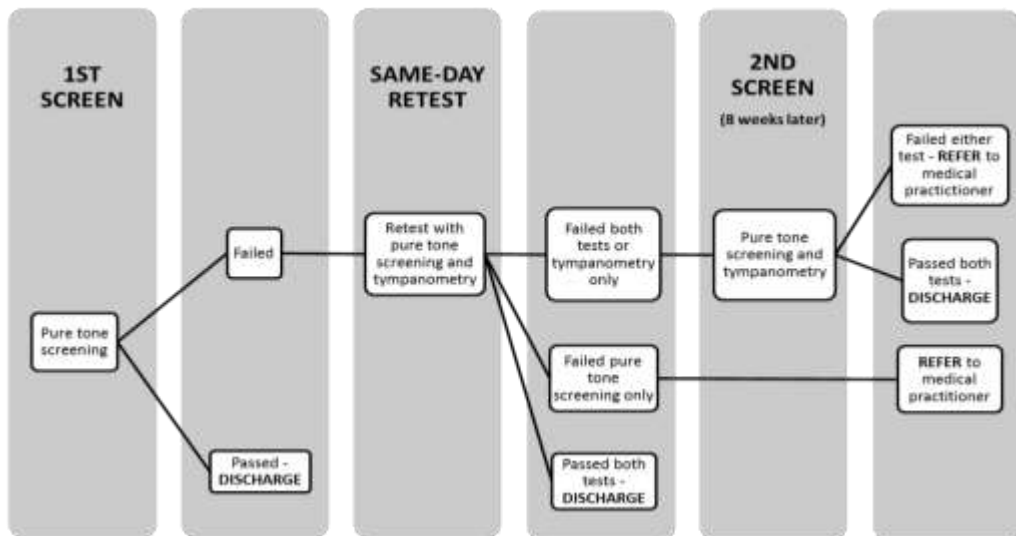


Figure 4.7. An example of a two-tiered hearing screening protocol based upon AAA (2011) recommendations.

Screening can be an almost useless endeavor if it does not lead on to diagnostic assessment and timely intervention. Unfortunately, receipt of follow-up care in school hearing screening programs has been not infrequently reported as sub-optimal. For example, Kemper, Fant, Bruckman, and Clark (2004), in their analysis of Michigan's program where 500,000 children are screened each year, found that only 73% of referred cases in grades 1-5 actually went on to receive follow-up services. This figure reduced to 57% for cases in grades 6-12. The most common reason cited by parents for failure to pursue follow-up was that the child had been previously evaluated for suspicion of hearing loss, followed by lack of concern, and doubt regarding screening accuracy.

To alleviate poor follow-up rates, AAA (2011) proposes: presenting results in the families' native language, including educational pamphlets on the effects of undiagnosed hearing loss, and propagating close relationships between screening personnel and the local

medical community. Mundy (2001) further suggests engaging school personnel to facilitate receipt of follow-up, staff that may assist those with transportation problems, with lack of information concerning local medical resources, with lack of medical/health fluency in general, and those with second-language related issues.

FUTURE CONSIDERATIONS

Screening for Central Auditory Processing Disorder

Central auditory processing disorder (CAPD) has caught the attention of researchers, clinicians, educators, and parents alike, with a Google search for “central auditory processing disorder” in 2013 bringing up over a quarter of a million hits. Despite this attention, screening for central auditory processing disorder (CAPD) is as controversial as the disorder itself, and with this in mind, this section will briefly review the definition of CAPD before considering the current evidence for its screening.

Defining CAPD

Despite several decades of research, we still lack *gold standards* for defining and diagnosing CAPD (Wilson and Arnott, 2012). This led Dawes and Bishop (2009, p. 440) to postulate that “APD, as currently diagnosed, is not a coherent category”. Through this controversy, the definition of CAPD offered by the American Speech-Language-Hearing Association’s (ASHA) Working Group on Auditory Processing Disorders Technical Report (ASHA [2005]; an update on ASHA [1996]) has come to be the most cited.

They define CAPD as “a deficit in neural processing of auditory stimuli that is not due to higher order language, cognitive, or related factors” (ASHA, 2006, p. 2), and as difficulties in the perceptual processing of auditory information in the CNS as demonstrated by poor performance in sound localization and lateralization; auditory discrimination; auditory pattern recognition; temporal aspects of audition, including temporal integration, temporal discrimination (e.g., temporal gap detection), temporal ordering, and temporal masking; auditory performance in competing acoustic signals (including dichotic listening); and auditory performance with degraded acoustic signals (ASHA, 2006, p.2).

While this is the definition of CAPD that will be used in this section, the reader should consider other definitions such as those offered by AAA (2010) and BSA (2011a).

Screening for CAPD

Efforts to identify children with CAPD have been driven by at least three main factors. First is the incidence of CAPD, which is estimated to be as high as three to five percent in school-aged children (Chermak and Musiek, 1997). Second is the potential impact this disorder could have on listening, communication, and academic success (ASHA, 2005). Third is the need for early intervention “to exploit the plasticity of the CNS, maximize successful therapeutic outcomes, and minimize residual functional deficits” (ASHA, 2005, p. 11).

While the motivation to screen for CAPD appears to be strong, agreement is lacking on the “who, when, and how” of this screening. The guidelines for screening offered by Wilson and Jungner (1968) suggest we should screen children at risk for CAPD, who have access to

appropriate diagnostic and treatment facilities at an affordable cost, who can be screened before CAPD becomes a problem or at least when they can benefit from intervention, and for whom we have suitable screening tools that can be applied by suitably qualified screening personnel.

Converting these principles into practice has remained a significant challenge, however.

Deciding who is at risk for CAPD has proven to be as controversial as the definition of CAPD itself. ASHA (2005, p. 5) state that individuals suspected of having CAPD frequently present with one or more behavioral characteristics, with their list being:

Difficulty understanding spoken language in competing messages, noisy back-grounds, or in reverberant environments; misunderstanding messages; inconsistent or inappropriate responding; frequent requests for repetitions, saying “what” and “huh” frequently; taking longer to respond in oral communication situations; difficulty paying attention; being easily distracted; difficulty following complex auditory directions or commands; difficulty localizing sound; difficulty learning songs or nursery rhymes; poor musical and singing skills; and associated reading, spelling, and learning problems.

They also warn, however, that this list is illustrative and not exhaustive, and that these behavioral characteristics are not exclusive to CAPD.

How to Screen for CAPD

Deciding how to screen for CAPD is difficult. ASHA (2005) states that while there is no universally accepted method of screening for CAPD, current screening approaches typically involve systematic observation of listening behavior and/or performance on tests of auditory function that probe auditory behaviors related to academic achievement, listening skills, and communication. In the absence of an appropriate tool for primary screening for CAPD, Bellis (2003) has argued that such screening should be left to parents and teachers who are best positioned to regularly observe the child’s behavior.

If a parent and/or teacher reported a child showed behaviors associated with CAPD, then Bellis (2003) recommends a secondary screening be conducted by a team of professionals that could include an audiologist, speech-language pathologist, educator, psychologist, social worker, the parents and a physician. The aim of this secondary screening is to gather information about the child’s central auditory processing *and* educational, social, speech/language, cognitive, and medical characteristics.

This aims to “provide a picture of the child’s strengths and weaknesses across domains” so that the team can decide if there exists “sufficient evidence to support the likelihood that a CAPD is present” (Bellis, 2003, p. 170).

Suspected CAPD then triggers a referral to an audiologist for a diagnostic CAPD assessment, whereas suspicions of other disorders triggers referrals to more appropriate professionals (e.g., to a speech-language pathologist if a language disorder is suspected, to a psychologist if a cognitive disorder is suspected, etc.). Such a team approach does need to be balanced with practical issues including timing and cost (BSA, 2011b), which has left many researchers searching for the best single tool or small group of tools to screen for CAPD.

Tools Used to Screen for CAPD

It is beyond the scope of this section to describe all of the tools that have been used to screen for CAPD. Instead, this section will consider some of the tools that have been widely used by audiologists in the US (Chermak, Silva, Nye, Hasbrouck, and Musiek, 2007) where the diagnostic criteria for CAPD had been clearly stated and the data had been published in the peer reviewed, scientific literature.

Four questionnaires that have been used to screen for CAPD are the Children's Auditory Performance Scale (CHAPS), the Fisher's Auditory Problems Checklist (FAPC), the Listening Inventory For Education-Revised (LIFE-R), and the Screening Instrument for Targeting Educational Risk (SIFTER). The CHAPS (Smoski, Brunt, and Tannahill, 1998) requires teachers and/or parents to complete 36 questions rating a child's listening behavior in different listening conditions. Reports that the CHAPS cannot separate children with or without CAPD (Dawes, Bishop, Sirimanna, and Bamiou, 2008; Drake et al., 2006; Lam and Sanchez, 2007; Sharma, Purdy, and Kelly, 2009; W. J. Wilson et al., 2011) are evenly matched by those that report it can separate children with or without CAPD (Dawes and Bishop, 2010; Ferguson, Hall, Riley, and Moore, 2011; Iliadou and Bamiou, 2012; Moore, Ferguson, Edmondson-Jones, Ratib, and Riley, 2010).

The FAPC (Fisher, 1976) requires teachers and/or parents to use a simple checklist to identify any of 25 auditory behaviors of concern. A single study has reported it cannot separate children with or without CAPD (Dawes et al., 2008).

The LIFE-R series includes: the Before-LIFE-R (Anderson, Smaldino, and Spangler, 2011c), which requires students to mark items that describe their classroom setting; the LIFE-R Student Appraisal of Listening Difficulty (LIFE-R SALD) (Anderson, Smaldino, and Spangler, 2011a), which requires students to rate how difficult they find it to listen in 15 different classroom environments; and the After LIFE-R (Anderson, Smaldino, and Spangler, 2011b), which requires students to mark items that describe how they would respond in six difficult classroom environments. Teacher versions are also available (the LIFE-R Teacher Appraisal of Listening Difficulty [LIFE-R TALD] [Anderson, Smaldino, and Spangler, 2011d] and the LIFE-R Teacher Checklist: Self-Advocacy and Instructional Access [Anderson, Smaldino, and Spangler, 2011e]). A single study has reported one of the original LIFE questionnaires contained only two items that could separate children with or without CAPD (Johnston, John, Kreisman, Hall, and Crandell, 2009).

The SIFTER series includes the Preschool SIFTER (Anderson and Matkin, 1996), SIFTER (Anderson, 1989) and Secondary SIFTER (Anderson, 2004), each of which requires teachers and/or parents to rate a child's performance on 15 aspects of academics, attention, communication, class participation, and school behavior in the classroom setting. One study reported the SIFTER's academics subscore could (Johnston et al., 2009) and one study reported the whole questionnaire could not (W. J. Wilson et al., 2011) separate children with or without CAPD.

The most popular screening test for CAPD has been the Tests for Auditory Processing Disorders for Children, now in its third generation (SCAN-3:C; Keith, 2012), which requires professionals trained in standardized assessments to present children with pre-recorded stimuli to assess a range of central auditory processing tasks including gap detection, auditory-figure ground, and competing words. One study reported the original SCAN (Domitz and Schow, 2000) and one study reported the second generation SCAN-C (Madison,

Hallberg, Anfinson, DeMaio, and Drake, 2005) could not separate children with or without CAPD.

Conclusion

Screening for CAPD remains controversial. Many screening tools have been offered and of the few that have been assessed the evidence for their use remains equivocal with no one tool standing out as a best candidate for screening for CAPD. Based on these results, it appears that two statements by AAA (2010, p. 13) on screening measures for CAPD should remain in place: 1. “While a number of questionnaires have been used to screen for CAPD ..., they generally have poor specificity, tend to over-refer, and have not been validated”, and 2. “Further studies are needed to determine the efficiency of currently available screening instruments, including the efficiency of diagnostic tests used for screening purposes, and to develop new screening tools for CAPD.”

Noise-Induced Hearing Loss

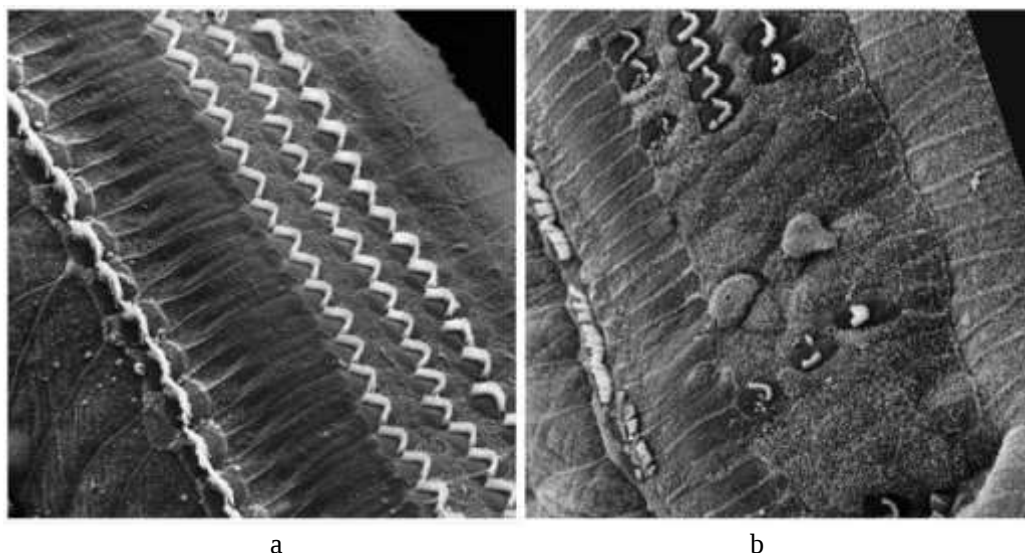
Recent research has drawn attention to the high prevalence of noise-induced hearing loss (NIHL) in adolescents, with preventative educational programs subsequently arising. For instance, the United States of America National Center for Health Statistics 2005-2006 NHAMES III data provided a prevalence rate of noise-induced hearing threshold changes of 16.8% (95% CI: 13.9%–19.7%) for adolescents aged 12 to 19 years (see Henderson, Testa, and Hartnick, 2011, for full details) and programs such as “Hear Today, Hear Tomorrow” a school curriculum based hearing health program by the National Acoustic Laboratories (www.nal.gov.au) and “Dangerous Decibels” by Oregon Health and Science University (www.dangerousdecibels.org) have been recommended to counteract this excessive occurrence of NIHL in older children. However, less is known about the prevalence of noise-induced hearing changes in younger, elementary school children. The Oregon Health and Science University’s Hearing Research Centre has accumulated data from over 30,000 cases during 2002-2011 to show that approximately 17% of 5-12 year children have a hearing loss of at least 20 dB HL at 4 kHz – an indicator of NIHL (<http://www.dangerousdecibels.org/research/omsi-research-data/>). AAA (2011) also reported unpublished data from three US school districts that showed that there was a trend for decreased identification of new hearing losses in grades 1-3 but an increased identification rate at grade 5, suggesting a possible increased prevalence of high frequency hearing loss in the upper grades of elementary schools. Moreover, the role that routine screening in elementary schools could play in the immediate and long-term prevention of NIHL has been under-researched to date.

NIHL results from exposure to hazardous noise levels, be they very high levels for short periods of time (e.g., 120 dB A for 30 seconds) or lower levels for longer periods (e.g., 90 dB A for 3 hours per day). The increasing use of personal listening devices, such as iPods and MP3 players, has been frequently implicated in the causation of NIHL in children (Hender-shot, Pakulski, Thompson, Dowling and Price, 2011; Niskar, Kieszak, Holmes, Esteban, Rubin, and Brody, 2001; Shargorodsky, Curhan, Curhan, and Eavey, 2010).

However, the World Health Organization (1997) have also noted that US children may receive more adverse noise exposure during a typical day at school than workers during an 8-hour factory shift. Such noise sources may include, but are not limited to: educational toys,

musical equipment, sound field amplification systems, concerts, theatre productions, trade equipment, computers with headphones, and traffic noise.

NIHL is produced due to permanent damage to the delicate hair cells of the cochlea (see Figure 4.8). It is typically progressive, with a gradual onset, and appears on the audiogram as a high-frequency notched pattern. That is, “dips” in the audiogram will be seen in the high frequencies, most notably at the test frequencies of 3, 4, or 6 kHz with recovery at 8 kHz in the early stages. Niskar and colleagues in 2001 reported that 12.5% of 6- to 19-year-old children in the US were estimated to display such a notch in at least one ear, with 6 kHz being the most commonly affected frequency (Sekhar, Rhoades, Longenecker, Beiler, King, Widome, and Paul, 2011).



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Figure 4.8. (A) Normal cochlear hair cells showing three rows of healthy outer hair cells (OHCs) and one row of healthy inner hair cells (IHCs), (B) damaged cochlear hair cells producing a sensorineural hearing loss.

As the condition progresses, hearing loss will extend into the lower and higher ranges (Meinke and Dice, 2007). At this point, the typical negative consequences of permanent childhood hearing loss may be experienced, including delayed/disordered speech and language development, learning difficulties, social and behavioral problems, and, ultimately, reduced quality of life.

A hearing screening protocol capable of detecting NIHL (or, for that matter, any other form of hearing loss that produces a high-frequency notched audiometric configuration, such as is seen in ototoxicity or head trauma) must include assessment of the frequency range from 3 to 6 kHz. If utilizing pure tone screening as the method of choice, this will necessitate a longer test time with potential reliability implications when testing the younger grades in non-sound treated environments.

In addition, screening failure rates can be expected to dramatically increase. Sekhar et al. (2011) noted that when utilizing a pure tone screening criteria designed for detection of NIHL, 26.4% of 296 eleventh grade students received a failing result. Program management

pathways would need to be carefully revised to deal with such a large proportion of follow-up cases – it would hardly be feasible to refer a quarter of all students for in-depth diagnostic testing. Schlauch and Carney (2010), in their examination of the NHANES III data, suggested that careful elimination of calibration errors, as well as utilizing headphones with low measurement variability, and repeating/averaging threshold measurements, may help to reduce the unacceptably high false-positive rate that could be associated with screening at 6 kHz.

An alternative to pure tone screening for NIHL may very well be the use of otoacoustic emissions to provide early detection of cochlear changes that occur prior to the advent of a measurable hearing loss (Meinke, 2011). Although further, extensive research is required regarding this application in elementary school settings, otoacoustic emission screening could serve as a useful adjunct to pure tone screening whereby, for instance, cases with normal pure tone results at the standard test frequencies of 0.5, 1, 2, and 4 kHz, but with abnormal otoacoustic emission SNRs at the frequency bands centered around 3 kHz, 4 kHz, and/or 6 kHz, would be marked for monitoring screens through time (perhaps on a yearly basis) and would receive preventative, educational counseling. A well-constructed computerized data management system (of the kind described in Chapter 11) would allow for easy analysis of changes in baseline measures.

Whilst true that NIHL is irreversible, its progression can be halted to a certain extent by avoidance of exposure to continual hazardous noise (Niskar, Kieszak, Holmes, Esteban, Rubin, and Brody, 1998). There is much scope for research to contribute toward hearing loss prevention at the earliest possible age and the investigation of otoacoustic emission protocols in elementary schools would be an obvious starting point.

Telehealth

Telehealth is the general term used to describe the application of medically-related services over a distance (Givens and Elangovan, 2003), typically associated with the use of telecommunication technology such as high-speed computer networks and the internet. Tele-audiology, providing audiological services using telehealth, has been studied by a few researchers using synchronous methods (where services are provided and results transmitted in real time) and asynchronous methods (where results are stored and forwarded for later analysis). Synchronous methods include the possibilities of (a) the audiologist utilizing interactive video to supervise a technician at a distant clinical site, then providing diagnosis and management recommendations or (b) the audiologist utilizing remote technology to directly test the case at a distant site, with the technician's role limited to headphone and probe placement, et cetera (Lancaster, Krumm, Ribera, and Klich, 2008).

Young and Ireson (2003) reported telehealth services in schools to be cost effective and highly acceptable to key stakeholders including parents, children, and school officials (Lancaster et al., 2008). Furthermore, Lancaster et al. (2008) conducted a thorough examination of the feasibility and test performance of a tele-audiology school hearing screening program. Forty-three third grade students in a Utah elementary school were screened by an audiologist on-site using otoscopy, tympanometry, and pure tone audiometry.

A second audiologist performed the tele-audiology screenings from a distance of approximately 30 miles, with the first examiner acting as a facilitator only. In the tele-

audiology model, video otoscopy and pure tone testing results were synchronously interpreted by the distant examiner, with tympanometry results being asynchronously forwarded and analyzed. Full agreement between results obtained on-site and those obtained via tele-audiology was obtained for all otoscopy and tympanometry findings. For pure tone testing, disagreement occurred for 5/43 cases, although such was not considered statistically significant. These cases included four false-positive responses and one false-negative.

Therefore, in this study, although sensitivity for pure tone screening was found to be very high, specificity was less than optimal. The researchers concluded that tele-audiology demonstrated great potential for application in the hearing screening of school-aged children and suggested that further research should be conducted with larger cohorts and over greater distances, with attention given to proper training of technicians/facilitators and adherence to telehealth privacy requirements.

Tele-audiology may prove to be a very useful alternative to traditional on-site hearing screening in schools, helping to increase the productivity of pediatric audiologists who are, in many countries, in short supply. It may reduce the inefficiencies and inequities associated with hearing health care services in rural and remote locations.

Finally, it may be found to offer an improvement in the accuracy of screening, as it has been noted that school hearing screenings are often plagued by non-standardized protocols and procedures, non-calibrated equipment, inappropriate noise levels, and performed by poorly trained staff (Blair, 1991).

Genetic Screening

As it currently stands, many professional bodies concerned with the genetic testing of children advise against genetic analysis for adult-onset conditions. For instance, The Committee on Bioethics of the American Academy of Pediatrics state that such testing in general should be deferred until adulthood or until an adolescent is capable of mature decision-making (Committee on Bioethics, 2001).

Similarly, the United Kingdom's Clinical Genetics Society considers predictive genetic testing of children inappropriate until they can make such requests for themselves, as autonomous adults (Clarke and Working Party of the Clinical Genetics Society, 1994).

However, as noted by Caga-anan, Smith, Sharp, and Lantos (2012), not all adult-onset conditions are alike. For some conditions, the early diagnosis offered by genetic testing may promote improved management of the condition or psychological benefits regardless of the test outcome. In these cases, the ethical case for early genetic testing is clear (Caga-anan et al., 2012).

Further, the American Academy of Pediatrics' expert committee on the subject (AAP, 2013) advises against school-based genetic carrier testing or screening programs as "the school environment is unlikely to be conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or appropriate counseling" (p. 621).

Currently, there are no known genetic screening programs available for operation in elementary schools. If programs of the like were to be devised, it would require extremely careful examination of the potential risks versus harms. Geneticists, genetic counselors, and bioethicists would be needed to determine the specific medical benefits, psychological risks

(including the impact upon the child and upon family dynamics), and personal histories of the cohort (Caga-anan et al., 2012).

At present, no discussions of this kind have been published in regard to genetic screening of elementary school children for markers of late-onset hearing loss. Future applications, if considered at all, perhaps may be related to genetic testing for susceptibility markers associated with age-related or noise-induced hearing loss, which is still a relatively new and unexplored field. The potential benefits of predictive genetic screening of this nature might include access to preventative education and new treatment strategies, such as gene therapy, pharmacological interventions, stem cell implantation, et cetera, which are designed to halt or slow the development of hearing loss.

However, prior to implementation in elementary schools, it is likely that this new direction will first be explored in relation to adolescent screening.

CONCLUSION

To instigate the detection and re/habilitation of undiagnosed hearing loss in children, school hearing screening programs are a necessity. They present as a useful adjunct to newborn hearing screening, especially for postnatal cases, where the loss is acquired, progressive, or late-onset, as well as for milder cases that may have been missed by the newborn screen, and for cases where newborn screening was not available or desired. However, significant planning is required in order to operate an efficient and effective school hearing screening program. This chapter has provided an overview of the main methods and protocols for school screening. It has also offered suggestions for alternative screening techniques and has highlighted some potential future directions that may improve the current state of school hearing screening programs. It is posed that further, rigorous research and evaluation will soon lead to vast improvements in this screening endeavor.

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Chapter 3

WORKING WITH LEARNERS WITH HEARING LOSS IN STEM

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ABSTRACT

Learners with hearing loss can acquire science, technology, engineering, and mathematics (STEM) knowledge and skills. There is evidence in history that several important inventions in STEM were made by individuals with hearing loss. The vast majority of young people with hearing loss come from families with no previous experience of raising children with hearing loss. It is argued that these families should be provided unbiased and clear information regarding all aspects of the development of children with hearing loss. With such information, they can make informed choices that will positively impact their involvement in early intervention programs for their children. Thus they will begin to lay the foundation for the development of STEM knowledge and skills in their children by being able to consistently communicate with them. The implications of utilizing educational materials and programs with rich visual effects such as videos, animations, 3-Ds, and subtitles; having effective teachers who plan and address the unique learning needs of learners with hearing loss; and supporting learners with hearing loss to be actively involved in their own learning process to facilitate the development of STEM knowledge and skills are discussed.

INTRODUCTION

In this chapter, important factors for understanding and enhancing the educational experiences, and outcomes for learners who have hearing loss in science, technology, engineering, and mathematics (STEM) are highlighted. Hearing loss is used in this chapter as a broad generic term for any hearing dysfunction that precludes successful processing of all

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linguistic information through the ears regardless of severity, etiology, and age of onset. Nonetheless, the different degrees of hearing loss: mild, moderate, severe, and profound clearly suggest that children who have hearing loss have different communication and educational needs (see for example, Gomez, Piehota, & Dischner, 2012; McKay, Gravel, & Tharpe, 2008) for a review.

In the United States, Canada, United Kingdom, and other Western countries, there have been concerted efforts toward developing strategies for addressing STEM and other educational needs of individuals with hearing loss over the past decades (Spencer & Marschark, 2010). This has been due to increased understanding of people with hearing loss, their communication methods, and ongoing changes and progress in pedagogy, psychology, psycholinguistics, and technology. Evidence suggests that more progress has been made in the education of children with hearing loss in the United States during the last 30 years than in the previous 300 years (Marschark, Lang, & Albertini, 2002).

Although history is replete with amazing feats of many famous individuals with hearing loss in STEM, for example, Thomas Edison's light bulb and thousands of other inventions; Sir John Warcup Cornfield, winner of the Nobel Prize in 1975 for his work in Chemistry and cholesterol; Robert Weitbrecht, inventor of the special telephone for deaf people (teletypewriter or TTY, for short); Annie Jump Ganon, in astronomy; to mention just a few (Deaf Scientist Corner, 2013); current evidence indicates that majority of learners with hearing loss have lower achievements in STEM compared to their hearing peers (Blatto-Vallee, Kelly, Porter, & Fonzi, 2007; Vosganoff, Paatsch, & Toe, 2011).

Consequently, new options and perspectives that could lead to achieving better outcomes for learners with hearing loss in STEM should be continually provided to families and their children with hearing loss, their teachers, and other professionals in the field. Controversies regarding the best strategies for instructions and services to achieve this goal, especially in terms of methods of communication, have continued to be prevalent in the field (Mukaria & Eleweke, 2010). Nonetheless, it is argued that learners with hearing loss can achieve success in STEM if such controversies are set aside, and efforts are focused on providing appropriate services that will foster their learning and cognitive development immediately following the diagnosis of hearing loss. Given that the majority of children with hearing loss in this country and other Western countries now live at home and are in inclusion educational programs due to numerous legislative mandates (Hyde & Power, 2003; Marschark, Sapere, Convertino, & Pelz, 2008) programs and services to enhance their educational development and subsequent success in STEM must begin immediately after the diagnosis of hearing loss. To effectively provide meaningful foundation for the success of children with hearing loss in acquiring STEM knowledge and skills, the following are important considerations: (1) supporting families, (2) appropriate and effective early intervention programs, (3) use of relevant technology and software, and (4) effective teaching strategies and study habits.

SUPPORTING FAMILIES TO PROVIDE STEM DEVELOPMENT SUCCESS

Majority of children with hearing loss in the United States, Canada, United Kingdom and most Western countries live at homes with their families due to legislative mandates supporting inclusion of learners with special needs in regular education programs in these

countries (see for example, Marschark, Sapere, Convertino & Pelz, 2008). Consequently, the foundation for the success of these children in all aspects of development including STEM must be laid at homes by supporting families. Evidence indicates that the vast majority of children with hearing loss, more than 90%, come from hearing families with no previous experience of hearing loss (Mitchell & Karchmer, 2004). With no previous experience of raising children with hearing loss, the parents could experience various devastating psychological reactions when the hearing loss was diagnosed and disclosed to them (Borum, 2012; Jackson, 2011). Without timely support, some parents could remain in denial and shopping around for a 'cure' for too long (Scheetz, 2012). There is a real danger that the child's developmental needs could be neglected if the adverse psychological reactions parents may experience by the diagnosis of hearing loss persisted for too long. These parents, therefore, require timely support and education regarding childhood hearing loss and its implications for the child's development. They need to know about the various communication and educational options for children with hearing loss (Marschark, 2007).

For parents to be effective in meeting the developmental needs of their children with hearing loss and ensure their success in all aspects of development including STEM, they should be empowered to take the initiative in seeking out programs and services that would foster the development of their children. To achieve this goal, families of children with hearing loss require clear and unbiased information on all the issues that are essential for the communication, educational, social-emotional and other aspects of the development of their children with hearing loss (Jamison, Zaidman-Zait, & Poon, 2011). Although the importance of providing such information is acknowledged in the literature, it seems to be the case that in many instances, parents may not receive such information (Eleweke, Bays, Gilbert, & Austin, 2008). The failure to provide clear and unbiased information has adverse consequences. For instance, a family's ability to adapt to the child's hearing loss may be hindered by the lack of information about available services. Evidence clearly indicates that many parents are still not receiving adequate information and support during the critical early development years, and many remain uninformed and unable to assist their children at home. Lacking information, many parents are unable to make appropriate choices about the communication and educational needs of their children (Davila, 2004).

Providing unbiased and clear information is the critical modality of supporting families with young children who have hearing loss to enable them to lay the foundation for the development of STEM knowledge and skills in young children with hearing loss. When unbiased and clear information is provided, they will be able to make informed choices that will address the STEM knowledge and skills and other developmental needs of their children. However, concerns remain about the nature of the information professionals provide to families. Evidence indicates that many parents are aware that they are not getting all the information they need, and that some of the information they receive is patently biased (Marschark, 2007).

Nonetheless, evidence is consistent that the provision of unbiased and clear information and support are critically important to enable families to participate actively in the development and education of their children with hearing loss (Eleweke, et al., 2008; Jamison, Zaidman-Zait, & Poon, 2011). The information and support provided to families could make the biggest differences in their lives by empowering them to take the initiative to seek services that would help them and their children (Turnbull, Turnbull, Shank, & Smith, 2004). This demands that the family-centered approach which calls for collective

empowerment rather than a more traditional relationship where the professional had power over the family should be utilized in sharing information and providing support to parents of children with hearing loss. With this approach, parents and family members must become essential partners in the decision-making process. Consequently, teachers and other service providers should consider the family constellation as the appropriate focal point of professional attention in providing information about developmental needs of children with hearing loss and supporting their families to follow through.

Using family-centered approaches will assist parents of children with hearing loss to acquire the information and supports they need in order to foster the STEM and other aspects of their children's development. For instance, a family's ability to adapt to the child's hearing loss may be facilitated by the provision of relevant information about available services. Equipped with appropriate information, support, and knowledge, many parents of children with hearing loss will be able to make appropriate choices about the communication and educational needs of their children, which will in turn facilitate the development of STEM knowledge and skills in the children. Evidence from the Colorado Home Intervention Program (CHIP) and studies in the United Kingdom indicated that families with young children with hearing loss could benefit immensely from programs provided within their homes (Yoshinaga-Itano, 2004). Parents could be visited by professionals such as teachers, speech and language pathologists, audiologists, early childhood special educators, bilingual educators, psychologists, and social workers. These professionals provide information about counseling, developmental assessment, communication, and educational options. Targets should be established for timing of initial visit by professionals to the family of a newly diagnosed child with hearing loss. The visits should be carefully planned and conducted with the goal of giving unbiased information and empowering parents so that they can make informed choices.

It is critical that professionals give contact information about local and national organizations concerned with hearing loss to the parents. These professionals, especially those with hearing loss, should be included in the team that makes the initial visit to families since they have first-hand experience of living with a hearing loss. Consequently, apart from providing information and mentoring families, they could give hope and inspiration to families and their children. Additionally, it is imperative that parents with newly diagnosed children have the opportunity of meeting and chatting with other parents who have been or are currently working their way through similar issues. These parents provide mutual and social supports to each other to cope better in meeting the challenges of raising a child with a hearing loss. Such parents manifest better behavioral interactions and greater sensitivity to their children's communication and other needs (Turnbull & Turnbull, 2006).

EFFECTIVE EARLY INTERVENTION PROGRAMS SUPPORTING STEM KNOWLEDGE AND SKILLS DEVELOPMENT

Given that the majority of parents of children with hearing loss are hearing people with no previous experience of raising children with hearing loss, it becomes imperative that following information and supports provided to the families to deal with their adverse reactions to the diagnosis of the hearing loss and obtaining understanding of what raising

children with hearing loss entails, effective early intervention measures should be established to foster the development of STEM knowledge and other skills in children with hearing loss. Effective early intervention services could greatly enrich the conceptual store of children with hearing loss. Through such programs, communication barriers posed by hearing loss could be dealt with as parents and family members are supported to learn how best to communicate with their children (Fulcher, Purcell, Baker, & Munro, 2012).

Timely initiation of early intervention services could prevent or greatly reduce the communication barriers posed by hearing loss (Holzinger, Fellinger, & Beitel, 2011). These services are necessary because of their focus on language development, parent-child communication, social skills, educational, cognitive and other aspects of development, and support for the utilization of any residual hearing the children with hearing loss may possess. All these areas are important for the development of STEM knowledge and skills in children with hearing loss. It has been argued that there is evidence of strong relationship between language skills, especially reading and writing, and performance on STEM tasks and assessments (Vosganoff, Paatsch, & Toe, 2011). Consequently, appropriate early intervention programs may provide parents with strategies for enhancing their children's language and educational development through sign language instruction, speech training skills, or both depending on the particular program (Kasai, Fukushima, Omori, Sugaya, & Ojima, 2012). The goal of early intervention must be to foster effective parent-child communication starting soon after diagnosis of hearing loss. This kind of communication is the best single predictor of success in STEM knowledge and skills and virtually all other areas of development of children with hearing loss, (Marschark, 2007). Clearly, effective interactions, with the most appropriate means of communication, between caregivers and the child will provide opportunities for involvement in most normal activities of childhood in both social and academic areas, which foster the development of STEM knowledge and skills.

Thus, an important goal of early intervention should be to provide children with hearing loss with the opportunity to acquire language in the appropriate modality (sign or spoken) by having accessible and competent language models. Consistent means of communication, in the appropriate modality that is congruent for the child, will create opportunities for positive social interactions critical for the social-emotional development and STEM educational success of all children including those with hearing loss. Evidence indicates that children with hearing loss who are identified early and participate in early intervention programs achieve significantly better language, speech, social, and emotional developments than those who are not identified early and who receive intervention at a later time (Fulcher, et al., 2012; Holzinger, et al., 2011). To provide effective early intervention for children and their families, the program should not be influenced by the controversy regarding the *best* communication approach that has characterized the field of education of children with hearing loss for decades. There seems to be a common agreement with Marschark (2007) that there is no single correct answer about the *best* or superior method of communication for children with hearing loss. These children are different and therefore their communication and other developmental needs will be different. Consequently, no one method can be applied to all or even most of them. The important thing is to establish, as early as possible, an effective mode of parent-child communication, one that the child can access fully (Calderon, 2000). This is the foundation for successful social, emotional, and academic, STEM knowledge and skills, and other aspects of development of children with hearing loss. Through objective

assessment, open-mindedness, and willingness to be flexible, the mode of communication that would be appropriate for each child could be found.

FOSTERING STEM KNOWLEDGE AND SKILLS USING INFORMATION COMMUNICATION TECHNOLOGY AND SOFTWARE

Over the decades there has been tremendous developments in the field of information and communication technology (ICT) that provide great benefits to learners with or without special needs. For many learners without special needs, learning materials on the internet, world wide web (WWW), CDs/DVDs, flash-drives, and so on support their independent learning. Using these resources, they can become self-directed learners. They can use these resources to learn in the school and at home. Unfortunately, the same cannot be said for learners who have hearing loss. Given the poor literacy skills of the majority of these learners, (Debevc & Peljhan, 2004; Vosganoff, Paatsch, & Toe, 2011), these ICT resources must be in forms rich with visual reinforcements. It has been argued that learners with hearing loss must be considered as visual learners (Moores, 2010). Consequently, educational materials and resources meant to foster STEM knowledge and skills that are based in print or spoken English or other national languages may be of very little benefit to the majority of learners with hearing loss who have poor skills with English literacy (Coppens, Tellings, Schreuder, & Verhoeven, 2013). Nonetheless, evidence suggests that ICT resources rich with visual elements can enhance the teaching and learning of STEM materials in learners with hearing loss (Debevc & Peljhan, 2004). According to these authors, the inclusion of visual or multi-media elements such as animation, videos, and subtitles in ICT-based educational materials and resources is mandatory to achieve the goal of enhancing STEM knowledge and skills in learners with hearing loss. These authors argue that these visual elements are appropriate for the visual abilities possessed by learners with hearing loss. Given that hearing loss creates challenges in mastering spoken and written English or other national languages, it is evident that these visual elements will greatly promote the acquisition of STEM knowledge and skills in learners with hearing loss. There is evidence that in some cases, learners with hearing loss will master materials and resources with the appropriate visual elements in less time than materials or resources lacking those elements (Debevc & Peljhan, 2004). It is clear then that ICT materials and resources that will facilitate the development of STEM knowledge and skills in learners with hearing loss must have these visual elements. Subtitles in English should be mandatory. Other elements such as animations and videos will be equally helpful. The assimilation of educational resources and materials with these visual and other interactive elements by learners with hearing loss will be greatly enhanced (Marschark, et al. 2008).

Clearly, multi-media visual elements will facilitate the acquisition of STEM knowledge and skills by learners with hearing loss in that the materials can be learned repeatedly in the school and at home. Due to legislative mandates, the majority of these learners live at home and attend day schools. Therefore, with ICT materials and resources rich with visual elements, easy and user-friendly interfaces, learners with hearing loss can repeatedly receive support in the school and from family members to learn and practice these materials and resources.

In addition to ensuring that resources and materials to facilitate the development of STEM knowledge and skills in learners with hearing loss have user-friendly visual interfaces such as videos, animation, and subtitles, the use of software specifically developed for this group of learners to facilitate their STEM learning and progress has been documented. For instance, Adamo-Villani and Wilbur (2010) reported two novel approaches to teaching mathematics and science concepts using 3-D animated interactive software for learners with hearing loss.

According to these authors, the content of the software program is based on the academic curriculum. This suggests that this software can address the material learners with hearing loss need to learn at different grade levels. There are animated characters constructed with the latest technology and design that use sign language in this software. This feature is particularly beneficial to learners with hearing loss who use American Sign Language (ASL).

EFFECTIVE TEACHING STRATEGIES AND STUDY HABITS ON STEM SKILLS IN LEARNERS WITH HEARING LOSS

As stated earlier, parents of children with hearing loss should be supported to understand these children's developmental needs. With this understanding, they could take actions that can lay the foundation for the development of STEM knowledge and skills in their children, for example, by learning how to communicate meaningfully with their children. Ultimately, these children will attend schools, pre-kindergarten (PK) to colleges and universities, where they must acquire deeper STEM knowledge and skills.

Do teachers of learners with hearing loss possess the knowledge and skills to effectively impact STEM knowledge and skills to these learners? This has been and remains an important issue in educating learners with hearing loss. With the enactment of legislation promoting education of learners with hearing loss and other special needs in regular schools in the United States and other Western countries, majority of learners with hearing loss attend regular schools, colleges and universities (Marschark, Sapere, Convertino, & Pelz, 2008). It could be the case that learners with hearing loss will need the support of sign language interpreters or captioning and real-time writers in the regular classroom. Concerns remain that even with these supports, learners with hearing loss in inclusive classrooms may be learning less than their hearing peers (see for example, Marschark, Sapere, Convertino, Seewagen, & Maltzen, 2004).

Experiments conducted by Marschark et al. (2008) indicated that the quality of instruction in terms of accessibility of the material offered to learners with hearing loss in inclusive environments is critically important to how well these students will understand and learn the materials. Given that learners with hearing loss may come to the classroom with lower literacy, metacognition, memory and problem-solving challenges when compared to their normally hearing peers, Marschark, et al. (2008) suggested that to effectively impact the desired knowledge and skills to learners with hearing loss, instructors will have "...exceptional teaching skills beyond their familiarity with the academic abilities and diverse learning styles of deaf students" (p. 558). The question then arises: Do teachers of learners with hearing loss at the various levels of education possess such exceptional teaching skills? Data to address this question are scarce.

Given that the majority of teachers at the various levels of education in inclusive settings may possess very little or no background training and experience in the methods of educating learners with hearing loss, it could be argued that very few teachers in inclusive settings possess such exceptional teaching skills. The implication of this could be that strategies to share information and skills about effective methods for teaching learners with hearing loss will have to be made available to teachers in the regular schools through various in-service training, seminars and workshops on a continuous basis.

Learners ultimately must take responsibility for their learning as they advance through the various levels of education. At the early stages PK – middle grades, a lot of support will be required from the parents or guardians. As learners advance through the various levels of learning, they will need to develop effective study habits in order to learn materials properly, and acquire the necessary knowledge and skills. Sulman and Naz (2012) have argued that effective study habits hold the key to the success of learners with hearing loss in acquiring STEM knowledge and skills. While the literature is replete with tips for effective study habits such as having regular times for study, studying in conducive environments, knowing how to make the best use of resources, making and reviewing notes, etc., the question remains: What is known about the study habits of learners with hearing loss? Data to answer this question are scanty. Learners with hearing loss are different in their degrees of hearing loss, family background, and experiences. Study habits are difficult to examine because as Marchark, Sarchet, Convertino, Borgna, Morrison, and Remet (2012) pointed out it is difficult to determine the veracity of responses to questions on this very personal issue. Nonetheless, evidence indicates that personal factors such as the ability to make effective use of resources such as support services, tutors, interpreters, student peers, and faculty could contribute to the success of students with hearing loss in institutions of higher education (Albertini, Kelly, & Matchett, 2012). Interestingly, areas of weaknesses identified by the deaf students involved in Albertini, et al. (2012) study include their inabilities to prepare for classes, manage their time, concentrate on assignments, identifying important information, preparing for tests and anxiety, motivation, and attitude.

According to Albertini et al. (2012) deaf “students reported high levels of academic difficulty compared to the national norms. They also expressed concern about their study habits, lower levels of verbal confidence, lower motivation to finish college, and less than positive attitudes toward teachers compared to the national norm group of typical entering college students” (p. 99). This implies that deliberate efforts must be made by schools and other educational authorities to explore strategies that will help learners with hearing loss to be aware of their own responsibilities for success in STEM and other areas of academics. Despite availability of abundant technological resources, personal effort is essential to acquire knowledge and develop mastery. It is suggested that adults with hearing loss who are successful in STEM should be identified in the communities.

There are certainly such people. With proper planning, it may be possible for such people to visit educational programs where learners with hearing loss are studying. Meeting, discussing with the students, and responding to their questions could inspire and motivate the students to cultivate the personal habits that will ensure their success in acquiring STEM knowledge and skills.

CONCLUSION

Supporting learners with hearing loss to be successful in STEM must begin immediately following the diagnosis of hearing loss. Given that the vast majority of parents of young children with hearing loss have no previous experience of raising such children, the starting point of the effort to ensure children with hearing loss develop STEM knowledge and skills must be the provision of unbiased and clear information and support to their families. This is necessary to assist the parents and other family members make the necessary adjustments to raising the child with hearing loss. With unbiased and clear information and appropriate supports, the parents could learn about all the resources that could facilitate the raising of their children with hearing loss available to them in the communities. Consequently, they will be aware of their responsibilities in ensuring the success of early intervention programs for the benefit of their children with hearing loss. Research suggests that timely instigation of early intervention programs will ensure that children with hearing loss achieve the same milestones in language development like their hearing peers. Poor literacy skills is one of the greatest challenges to learning STEM materials by learners with hearing loss. Thus the goal of early intervention programs is to ensure these children are successful in language development. In this context ‘language’, means whatever mode of communication that works for each young person with hearing loss. While a few may, with technology such as cochlear implants, and extensive speech and language therapy services, develop spoken language skills, the majority of children with hearing loss may not develop such language skills regardless of the technologies and services provided. It is very important that professionals in the field provide unbiased and clear information about all the issues in language development of children with hearing loss to their parents. Spoken language is one form of communication. Using manual methods is yet another. The focus must be that the method of communication that is effective with children with hearing loss is consistently used at home and school. This will foster learning and enrich the child’s conceptual store. With a consistent medium to communicate and learn, the child with hearing loss will be able to make progress in all aspects of development including acquiring STEM knowledge and skills.

Progress in science and technology is resulting in the development of programs and software rich with visual effects – videos, animations, subtitles, 3-D, etc., that can facilitate the acquiring of STEM knowledge and skills by learners with hearing loss. Nonetheless, given that the majority of children with hearing loss live at homes and attend regular schools due to legislative mandates, it remains a concern whether the teachers in inclusive classrooms are able to utilize these technological resources for the benefit of learners with hearing loss. Many of these teachers may have very little or no background knowledge about educating children with hearing loss and the special ICT resources that could enhance their education. In a very large class in a regular classroom there may be just one or two learners with hearing loss. These students may have a sign language interpreter. The interpreter is a professional trained to facilitate communication between the teacher and students with hearing loss and not a ‘teacher’. It remains the task of the teacher to ensure that learners with hearing loss access and comprehend the materials being taught. It is imperative that general education classroom teachers should be made aware of these technological resources that can facilitate the acquisition of STEM knowledge and skills in learners with hearing loss. This can be achieved by regularly conducting in-service training for these teachers by experienced

teachers of learners with hearing loss. It is possible that through this activity, teachers in inclusive programs will become very aware of the unique needs of students with hearing loss in their classrooms and always plan to address such needs. Otherwise, there is real danger that the needs of learners with hearing loss in inclusive classrooms will not be met. Consequently, acquiring the knowledge and skills in STEM and other academic areas will be problematic.

Finally, as learners with hearing loss advance through the various levels of education, it may be necessary for them to be provided mentors who will be working with them and reinforcing the development of effective study skills. Intrinsic motivation is necessary for academic success. Thus some learners with hearing loss may benefit if they have mentors who check-in with them, discuss their challenges and progress. Especially beneficial will be mentors who are successful in STEM and who have hearing loss themselves. These will make wonderful role-models as well as inspire and encourage young learners with hearing loss. It may be the case that education authorities will set up a program focused at identifying such successful role-models with hearing loss. With proper planning, many of such people may be glad to visit schools, meet and discuss with learners with hearing loss on a voluntary basis.

Taken together, learners with hearing loss can, with the appropriate supports starting immediately after the diagnosis of hearing loss, acquire STEM knowledge and skills. History is replete with successful people in these fields who had hearing loss. Given continuing progress in science and technology and development of innovative, user-friendly, multi-media educational programs and materials almost on a daily basis, learners with hearing loss can be very successful in acquiring STEM knowledge and skills and be able to contribute to the development of society.

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Chapter 4

HEARING AND COGNITIVE OUTCOMES OF COCHLEAR IMPLANTATION IN THE ELDERLY

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ABSTRACT

At the present time, 50 to 60% of the population above 70 years of age suffers from a hearing impairment and from 0.6 to 1.1% has a severe to profound loss, which cannot benefit from an hearing aid. Moreover, it is expected that this prevalence will grow by more than two-fold in the next 40 years. There is strong evidence that hearing loss in older adults is associated with both cognitive load and social isolation, which in turn, are associated with cognitive and physical functioning. Cochlear implant (CI) dramatically improves sound audibility and speech understanding. The aim of this paper was to analyze outcome and complications of CI treatment in elderly patients.

A retrospective study on 25 patients, aged at implantation between 65 and 79 years (mean = 70.03 ± 3.53), unilaterally implanted for severe to profound bilateral hearing loss. The following data were statistically evaluated: pre-implant pure-tone threshold and tests of speech recognition, both with hearing aid that without; post-implant threshold and speech perception with CI off and on. Moreover, statistical correlations of PTA improvement between two age groups (65 to 70 and over 70 years) were carried out.

Mean PTA improved from 113.86 (pre-implant) to 41.78 (post-implant); and the mean SRT improved from 90 dB to 56.06 dB. Moreover there was no statistical difference in PTA improvement between the two age groups (65 to 70 and over 70 years).

The comparison between speech perception threshold and cognitive-motivational status shows negative correlation with the cognitive test and, but a positive correlation with the depression test.

In the elderly, CI is a safe procedure that significantly improves hearing threshold ($p < 0.01$) and speech perception ($p < 0.01$). Support of family and professionals, as well as duration of deafness and pre-implant scores greatly influence the results of rehabilitation and its perceived benefit. CI should not be denied in older individuals who are otherwise in good health.

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Keywords: cochlear implant, hearing loss, elderly, cognitive deterioration

LIST OF ABBREVIATIONS

CI	Cochlear Implant
PTA	Pure Tone Average
SDT	Speech Detection Threshold
SRT	Speech Recognition Threshold
MOCA	Montreal Cognitive Assessment
GDS	Geriatric Depression Scale

INTRODUCTION

At the present time, 50 to 60% of the population above 70 years of age suffers from a hearing impairment and from 0.6 to 1.1% [1,2] has a severe to profound loss, which cannot benefit from an hearing aid. Moreover, it is expected that this prevalence of hearing loss in the elderly will grow by more than two-fold in the next 40 years.

Presbycusis has been attributed to degeneration of a component of the auditory system, both central and peripheral. The peripheral location of damage can be sensory epithelium, spiral ganglion or stria vascularis; Schuknecht proposed a classification system with three major forms of age-related loss-hearing, namely sensory, neural, and strial presbycusis. [3]

The central pathways of the auditory system are frequently involved with a slowdown of the information transmitted; the less the quality of the peripherycal data is detected, the more the processing at the central level has distortions.

Profound hearing loss among the elderly people is responsible for a significant reduction in quality of life due to social isolation, increased dependence, anxiety and depression that may contribute to the worsening of the cognitive and physical functions [4]. Auditory rehabilitation of the profound hearing impaired elders is important and, to date, cochlear implantation is the most effective procedure.

Individuals with a mild, moderate and severe hearing loss had a two-, three-, and five-fold increased risk of developing incident dementia, respectively, compared to normal-hearing individuals [4]. Moreover, analyses of the association of hearing loss with self-reported falls demonstrated that a 10 dB increase in hearing loss was associated with a 1.4 fold increased odds of having a fall. A 25 dB hearing loss was associated with a nearly three-fold increased odds of a fall over the preceding year. These results were substantively unchanged after adjusting for demographic and cardiovascular risk factors as well as vestibular balance function [5].

It is well demonstrated that cochlear implant (CI) dramatically improves sound audibility and speech understanding for the elderly patients, similarly to the young implanted patients. CI was a significant surgical innovation in the 20th century and represented the first artificial sensory organ applied in clinical medicine.

It was previously thought that CI in the elderly may not be beneficial because of age-related degeneration of both the central and peripheral auditory systems, surgical risk, and

overall cost to benefit ratio. However, recent studies have shown that this procedure improves auditory performance, is well tolerated even in the most elderly, enhances self-confidence, reduces in most cases tinnitus and stress and increases the health-related quality of life. The risk of anesthetic and surgical complications remains low provided that a thorough multidisciplinary evaluation is performed before the procedure.

The cost-effectiveness still remains acceptable, including patients over 70 [6] because even if healthcare costs are high, the savings in terms of indirect costs and quality of life are important. Among patients with pre-implant severe tinnitus, a partial or total tinnitus reduction was observed in 70% of cases [7].

Aim of this study was to evaluate audiological and cognitive outcomes in a group of 25 elderly subjects with cochlear implant.

METHODS

This is a retrospective study of 25 consecutive post-lingual, profoundly hearing impaired elderly adults selected among the overall 376 patients who were implanted at Padua ENT-Ear Surgery Department between May 2010 and February 2014. Selection criteria were age ≥ 65 yrs at surgery and unilateral implantation. Pre-implant evaluation consisted of pure-tone audiometry and tests of speech recognition, both with hearing aid that without. Post-implant evaluation included the same tests with CI off and on, carried out with free field stimulation in a sound proof booth. Threshold evaluation were conducted by using pure-tone average (PTA), that is the mean of the air-conduction thresholds at 500, 1000 and 2000 Hz. On the other hand, in the analyses of speech perception we considered the Speech Detection Threshold (SDT) and Speech Recognition Threshold (SRT). SDT corresponds to the value of sound intensity at which the verbal message is not understood but perceived as generic sound, therefore with a percentage of intelligibility of 0%. The SRT indicates the level of intensity at which the patient correctly repeats 50% of the words.

Cognitive functions and motivational status were assessed using the MOCA (Montreal Cognitive Assessment) and GDS (Geriatric Depression Scale) tests.

The results obtained were correlated with post-implantation PTA (pure tone average 500-1000-2000 Hz) and speech perception threshold (50% of speech recognition). We also correlated MOCA and GDS scores obtained among cochlear implant users.

Surgical outcome looked at the presence of any medical or surgical complication related to the implant surgery or to the age of these patients. Furthermore, the personal satisfaction degree was evaluated with a specific questionnaire developed at our clinic.

RESULTS

Our sample is composed by 25 patients (13F - 12 M) aged at implantation between 65 and 79 years (mean = 70.03 ± 3.53), that represents a 6.6% of our cochlear implantations during the considered period. Based on our experience, with respect to younger CI-recipients, this group of elderly had a higher incidence of associated comorbidities such as arterial hypertension, cardio-vascular diseases, usage of anticoagulants. Despite this, no surgical

events or complications with the anesthesia were observed and there was no need for additional intensive postoperative care.

The duration of hearing loss ranged from 1 to 50 years: 12 patients were deaf from ≤ 15 years and 13 were deaf from > 15 years. The etiology was unknown in the majority of cases (52%), while the most frequent known cause was otosclerosis (32 %).

Table 1. General information of implanted patients

Patient	Sex	Age implant (years)	Date implant	Side	Aetiology	Duration hearing loss (years)
1	M	66	28/05/2010	L	otosclerosis	15
2	F	72	05/11/2010	L	unknown	10
3	M	70	07/12/2010	R	unknown	15
4	M	68	18/03/2011	R	trauma	1
5	F	72	05/04/2011	L	unknown	9
6	F	77	19/05/2011	L	unknown	45
7	F	72	22/07/2011	R	unknown	30
8	M	71	14/09/2011	R	otosclerosis, trauma	8
9	F	73	02/11/2011	L	unknown	30
10	F	67	29/02/2012	L	neurinoma, trauma	30
11	M	72	13/03/2012	L	unknown	15
12	F	66	25/07/2012	L	otosclerosis	40
13	F	66	07/09/2012	L	otosclerosis	15
14	M	69	17/10/2012	L	otosclerosis	30
15	M	79	05/10/2012	R	unknown	50
16	M	65	08/02/2013	R	streptomycin	50
17	F	73	27/02/2013	R	unknown	18
18	M	65	18/04/2013	R	unknown	15
19	M	67	18/07/2013	L	otosclerosis, neurinoma	10
20	F	70	20/09/2013	L	otosclerosis	30
21	F	72	27/09/2013	L	unknown	13
22	M	72	17/10/2013	R	otosclerosis	40
23	M	69	13/12/2013	R	unknown	50
24	F	70	12/02/2014	L	unknown	30
25	F	68	13/02/2014	L	device-failure	15

First examination occurred one month after initial switch-on and programming of the speech processor (“activation”), followed by a second exam at 4 months, then at 7, 11 and 15 months. Many of our elderly patients expressed initial disappointment, during the first switch-on session, mainly due to the novel sound quality provided through the electrical stimulation, but also due to the initial lack of benefit. However, all patients have adapted and over time becoming regular daily CI users.

PTA values were compared between pre- and post-implant exams demonstrating a significant improvement with CI.

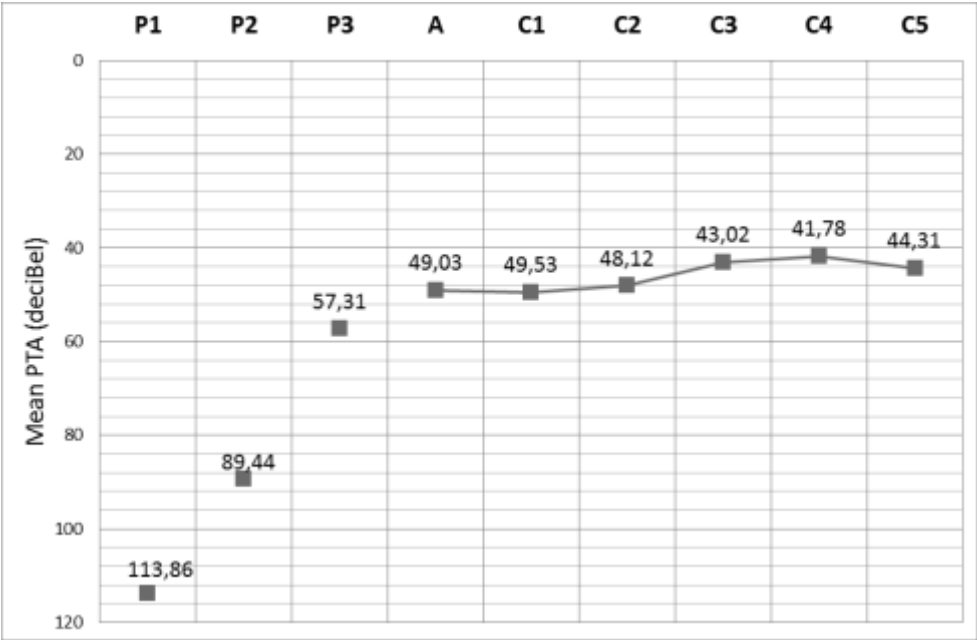


Figure 1. Pre- and post-operative PTA (P1=pre-op, side implanted; P2=pre-op, free field without hearing aids; P3=pre-op, free field with hearing aids; A=post-op at activation; C1=post-op, 1st control; C2=post-op, 2nd control; C3=post-op, 3rd control; C4=post-op, 4th control; C5=post-op, 5th control).

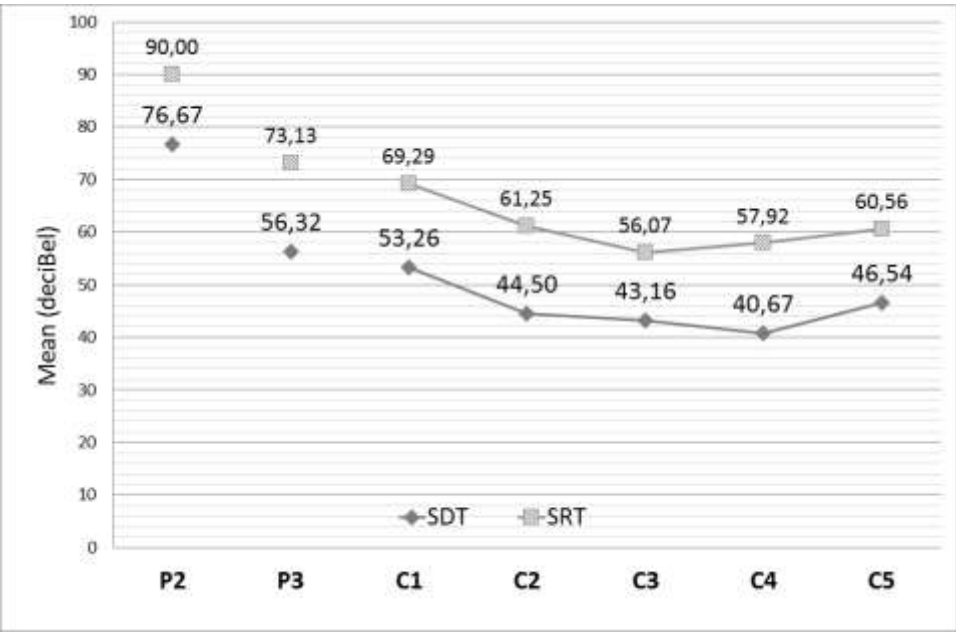


Figure 2. Pre- and post-implant mean speech detection threshold (SDT) and mean speech recognition threshold (SRT) (P2=pre-op, free field without hearing aids; P3=pre-op, free field with hearing aids; C1=post-op, 1st control; C2=post-op, 2nd control; C3=post-op, 3rd control; C4=post-op, 4th control; C5=post-op, 5th control).

Also speech perception scores showed a significant improvement both in the detection threshold (SDT) that in perception threshold (SRT). These variables were analyzed using descriptive statistic, Student t test ($P < .01$) and Pearson test ($P < .05$).

Dizziness was the most common temporary complication and was observed in 5 cases (20%). It was not correlated with the pre-op morbidities of the affected patients and was resolved within a few days in post-op for all cases. One transient-incomplete facial nerve weakness was found 3 days post-surgery and completely resolved in a few days.

CONCLUSION

Our results demonstrated that CI in older adults is a safe procedure, which significantly improves hearing threshold ($p < 0.01$) and speech understanding ($p < 0.01$). In particular, mean PTA improved in our patients from 113.86 (pre-implant) to 41.78 (post-implant); and the mean SRT improved from 90 dB to 56.06 dB. Our data are similar to those reported by Skarzynsky *et al.*, [8] and by Luntz *et al.*, [9], who evaluated an elderly population of similar age with respect to our (mean age at implantation respectively of 67.2 yrs and 66.7 yrs). In fact, these authors observed mean word recognition scores increasing respectively from 17% (pre-implant) to 66% (post-implant) and from 18% to 60%. By comparing these results with those of children and young adults implanted at our center during the same period, we observed that the elderly need a longer rehabilitative period, but eventually all of them were regular CI users and reached similar good results. Major post-CI complications were not encountered in this cohort. Post-implantation vertigo was not as significant as might be expected in this age group.

The present pilot study shows a strongly negative correlation between MOCA and speech perception threshold and a weakly negative correlation between MOCA and age. Furthermore, the results obtained confirm a strongly negative correlation between MOCA and GDS, and a positive correlation between GDS and speech perception threshold, in terms of stimulation levels (dB SPL) necessary to achieve a 50% of speech recognition.

The comparison between the MOCA scores and PTA values revealed a weakly positive correlation (Pearson = +0.31; p value = 0.68). The same correlation was found between GDS and PTA (Pearson = +0.31; p value = 0.68).

In our experience, support of family and professionals, as well as duration of deafness and pre-implant scores greatly influence the results of rehabilitation and its perceived benefit. In conclusion, we strongly recommend that CI should not be denied in older individuals who are otherwise in good health.

The preliminary results of the present study indicate that cochlear implant outcomes are better when cognitive and mental status of the patient is less deteriorated. Nevertheless, the correlation between age and cognitive assessment is not as strong as we expected. It's reasonable to obtain good results even in very advanced age. The patient's depression can affect both cognitive status and outcome with cochlear implant. The PTA seems to be important for the evaluation of cochlear implant positioning; nevertheless it is not sufficient for a good prediction of the speech recognition threshold.

In conclusion, cochlear implantation has proven to be a safe procedure, with low morbidity and complication rate even in the elderly patients that can obtain a significant

improvement in the auditory performance and quality of life. Counseling, auditory rehabilitation, speech training, psychological motivations, family support, mental and cognitive status are important aspects that can influence the outcome of cochlear implantation.

Competing Interests

The authors declare that they have no competing interests.

All the authors had given final approval of the version to be published.

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Chapter 5

EFFECTS OF IMPULSE NOISE ON HEARING IN MEMBERS OF THE POLICE SPECIAL OPERATIONS BATTALION

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ABSTRACT

This chapter presents a study of members of the Military Special Operations Battalion. This study, aiming for the deployment of a Hearing Preservation Program, analyzed the effects of impact noise on the hearing of military personnel who regularly conduct shooting practice. It was a case-control study with 115 military personnel, with 65 being exposed to noise from firearms and 50 not being exposed. Assessment of noise emitted by firearms was performed during shooting practice was carried out, and research on the knowledge about hearing health was measured. Pure tone audiometry and (transient and distortion product) otoacoustic emissions testing was also conducted. The results show that the level of noise emitted by firearms exceeds the limits established by regulatory standards. Also it was shown that despite the military personnel's having knowledge as to the importance of using hearing protection when exposed to weapons noise, many never received guidance on its proper use. And there are still significant differences in the hearing of those exposed to firearms noise when compared to those who are unexposed. For this population, it is necessary to implement a Hearing Preservation Program with the goal of not only to avoid hearing loss, but also to educate these military personnel on the importance of proper use of hearing protection and other hearing care issues.

INTRODUCTION

The main characteristic of the military profession is to live with risk, whether in training, daily life, or war. These professionals are subject to the strict precepts of hierarchy and discipline, absolute dedication, continuous availability, physical force, and constant

professional improvement. Even during inactivity and paid reserve time, military professionals remain bound to their profession and ready to serve upon being summoned to return to active duty, despite restrictions on labor rights [1].

In Brazil, after graduation from training, soldiers are placed in military units within the federal states, according to their characteristics and specialties. One is the Special Operations Battalion (BOPE). This Battalion was formed in 1977, originally named Company of Riot Police. It was remodeled in 1988 and went on to perform specialized police actions, being subdivided into three units: K9 (in charge of police dogs and search training), Special Operations Command (COE) and Specialized Public Patrols (RONE) [2].

RONE is prepared to combat violent crime such as robbery, kidnapping and drug trafficking. It uses midsize cars, weapons and special equipment, and camouflaged uniforms. This subunit has the mission to control civil unrest, urban and rural guerrilla warfare, occupation, and the defense and recovery of sensitive locations. It operates in locations where there are higher rates of violent crime. It is high risk duty, with operations such as raids, blockades, escorts, and sieges. Comparatively, COE is a small group of police officers specially trained for hostage situations, situations involving heavily armed groups, or where there is a need for special equipment and weapons. It is a similar squad to U.S. SWAT (Special Weapons and Tactics), a period of training and selection is necessary. It consists of teams of negotiators (psychologists), assault police (location and identification), snipers, and bomb disposal personnel [2].

When the personnel enter the Brazilian military, regardless of the unit in which they will serve, they must take the Shooting for Police course, which teaches the use of firearms. Taught in the course are theoretical concepts and definitions of arms and weapons, weapon types, ignition systems, weapons operation, and the characteristics of each weapon [3].

There is also a number of hours required for shooting practice, which varies with each course or each state. In the course of military personnel training in the State of Paraná, for example, over the three-year course, trainees log a total of 120 hours of classroom instruction and 160 hours of shooting practice [4].

In the disciplines of “Shooting for Police”, taught in the various courses of the Military Police of Paraná, shooting instructors are responsible for all theory and practice. In 2009, a book was published with some specifications addressed in disciplines such as the history of firearms, safety rules, generalities and types of weapons, ammunition, explosives, chemical weapons, shooting accidents, personal protective equipment (basic equipment, bullet-proof vests, helmets, shields, and vehicles) and police equipment (holster, belt, baton, handcuffs, knives, etc.) [5].

With regard to personal safety, one of the rules is to always use personal protective equipment during training. This equipment is mandatory by all who are participating in shooting instruction, for students as well as assistants and instructors. The devices mentioned are: goggles, earmuffs, and bullet-proof vests. Gloves, knee pads, elbow pads, helmets and gas masks are not mandatory.

In the internal arms manual used in the training course for military police officers in the state of Paraná, some guidelines are given regarding earplugs as protection from exposure to loud noise [6]:

- The placement, size and fit of hearing protectors should be comfortable.
- Use with glasses or other equipment can prejudice the seal with the face.

- Earplug can be moved or misplaced while shooting practice or even due to jaw movement.
- Deterioration of the ear protector, which is natural, with cracks or hardening of the plastic parts.
- Wear of the hearing protector pads, which can make the device loose, damaging the noise seal. Frequent inspections are necessary to prevent degradation of attenuation.
- Ear protectors must be worn during all instruction.

These topics are passed on to the trainees, emphasizing the need to keep their hearing intact, because of the daily dangers that officer's face. In this way, it is necessary for the police officers to become aware of the importance of safety by breaking with some beliefs that associate the use of hearing protection as weakness, this behavior being a cause of bias in the military [6].

Upon entry into the military, the officer does not have laws or regulations that require them to perform periodic medical examinations. They are only done when conducting ongoing training or postgraduate specializations for promotion. In the selection for inclusion in the COE, for example, one of the medical examinations required for admission is to have a hearing exam by audiometry. The exam, however, need not be conducted by military police, and may be done elsewhere.

Most of the courses and competitions for the military police always require an audiogram as a necessary condition [7]:

“(...) suitable candidates are those who are experiencing hearing loss in either ear of up to 20 dB HL at frequencies of 500Hz and 1000Hz; 30 dB HL at a frequency of 2000 Hz and 35 dB HL at frequencies of 3000 to 8000 Hz, for air and bone conduction.” (Item No. 14.1.12)

Hearing is considered important for entry into a military career, however, there is need for greater attention to hearing health during military that career, especially for those who are exposed to firearms noise, such as members of the Military Special Operations Battalion. This is because periodic medical examinations do not require auditory exams.

STUDY ON HEARING OF THE MILITARY POLICE

The study was conducted with police officers belonging to BOPE (exposed group) and compared with the administrative sectors of the Military Police of Paraná (non-exposed group).

Administrative sectors make up a large part of the Military Police force, with about five thousand personnel distributed among the units. BOPE currently has approximately 250 members, with 23 members in the COE.

The sample consisted of 115 police officers, divided into two groups.

Exposed group: 65 members of the riot police (43 from RONE doing shooting practice once a month or less, and 22 from COE that doing shooting practice weekly or fortnightly). There was no significant difference between average age and average hearing thresholds of these two subgroups.

Non-exposed group: 50 military personnel who work in administrative sectors of the Military Police force. These officers had not been exposed to firearm noise for more than twelve months.

The mean age of the exposed group was 32.2 (23-44) with a mean of 9.1 years of service (1-25 years). The subjects of the non-exposed group had a mean age of 33 (23-46) with a mean of 11.1 years of service (1-24 years). There was no significant difference when comparing the groups in age ($p = 0.5165$) and length of service ($p = 0.1136$).

RESEARCH PROCESS

The research was divided into 3 stages: (1) an assessment on the noise level for the weapons used, (2) a survey on the knowledge of the officers regarding the preservation of hearing health, and (3) an evaluation of the auditory profile of police officers exposed to impact noise, comparing this group with police not exposed to noise.

1) Noise Level for Firearms

The noise measurement for the weapons used by BOPE was performed in a training facility, both outdoors and indoors (in a bunker made of tires) (Figures 1 and 2).

The evaluation was performed with a Bruel&Kjaer sound level meter model 2230 and adjusted to perform the measurements of the peak level, on the C weighted, fast response, linear, and impulse settings. With the microphone placed inside the auditory zone of the shooter.

The assessment of the noise level reached the maximum limits of the equipment when measured in linear mode (peak dB SPL). For the dB (C) mode, the response for impact had a variation from 119 to 133dB (C).

The levels found are similar to the literature, ranging from 113 to 147dB (C) [8-11]. These results exceed the limits of Norm 15 indicating the tolerance threshold for impact noise intensity as 120 dB (C), and also the maximum number of impacts per hour, taking into account the intensity, is much higher than advised by the Standards for Occupational Hygiene by Fund a centro, which does not tolerate exposures above 127dB (C) [12-13].



Figure 1. Noise measurement .40 pistol.



Figure 2. Bunker made of tires and a Grenade.

2) Knowledge about Hearing Health by Police Officers

The police filled out a questionnaire with open and closed questions about their auditory history, auditory symptoms, and insights pertaining to hearing.

Regarding the use of hearing protectors during shooting practice, most police officers always use hearing protection in shooting practice, with the plug-type models being the most commonly used, and which are purchased by the officers themselves, but are not specific to military use. It was also noted that many never received information on the use of these devices (Table 1).

The hearing protectors provided by the force for use at marksmanship training sites are the earmuff type with no record of make, model or NRR (noise reduction level). They have no quality control or periodic evaluation on the effectiveness of these devices. Each police officer, however, has free choice to use any other protection that maybe acquired outside the force.

In relation to police officer knowledge and perception about noise, the majority (92.3%) reported using hearing protection during shooting practice, and most use the plug type (70.7%).

On the guidelines received about the use of hearing protection, most reviews said that the guidance received was superficial (38.4%), and 32.3% reported having never received guidance. When asked who directed the use of the ear protection, most reported receiving instructions from superiors (47.6%), while few reported having received information from specialized professionals (12.3%) (Table 1). Upon verifying the instruction received and the subsequent use of hearing protection, the effectiveness of such instruction is called into question because low frequency of use.

The use of hearing protection is the responsibility of superiors, but its effectiveness depends on the military personnel exposed to noise. There are reports of the use of other devices that were not hearing protectors, such as fingers, cotton, and empty ammunition cartridges. The ability of these devices to act in preventing NIHL is questionable. Even the

placement of hearing protectors is often inefficient to prevent damage to the auditory system, leading to permanent and progressive symptoms [8, 14].

Table 1. Use of hearing protection for shooting practice by noise exposure group (n = 65)

Hearing Protection	Absolute Frequency (n)	Relative Frequency (%)
<i>Frequency of use</i>		
Always	60	92.30
Usually	3	4.61
Sometimes	2	3.97
<i>Type used</i>		
Plugs	46	70.76
Earmuffs	7	10.76
Earmuffs + Plugs	11	16.92
<i>Use</i>		
Shooting range practice	46	70.76
Shooting range and outdoor practice	15	23.07
All noisy situations	12	18.46
Always when there is shooting	5	7.69
<i>Instructions given</i>		
Never received	21	32.30
Superficially	25	38.46
Only when enlisting in the police	8	12.30
Well instructed	8	12.30
Periodic updates	3	4.61
<i>Instructor</i>		
Military superiors	31	47.69
Communication materials	12	18.46
Specialized professionals	8	12.30

It is recommended that every military officer have his own hearing protection equipment, as is the case with bullet-proof vests and helmets. It is known that there is a resistance in the military to the use of hearing protectors, especially in external service and in combat, and there is no motivation from military superiors to do so, since many believe that the use of hearing protection jeopardizes the safety of personnel [15, 16].

A survey of occupational risk management in the Brazilian Army found that the question of the use of hearing protection is addressed superficially and it is left to the responsibility of instructors to pass on, or not, the relevant information. Therefore it is up to the population that performs shooting practice, to have guidelines that are more meticulous about using hearing protectors [8].

To check if there was knowledge about the hazards of noise exposure on hearing, there was an open question asking about what the effects of noise exposure on health for both BOPE members and to administrative services members. There was a significant difference ($p = 0.0034$) between the groups in terms of knowledge of the noise to cause hearing loss, showing greater knowledge in the population exposed to noise. This demonstrates that the exposed group has more contact with questions about noise, even being required to wear

hearing protection during shooting practice. When asked about the best form of protection against noise, 96.9% of the exposed police officers reported that the use of hearing protectors is the best way, compared to 68% of the non-exposed group. There was a significant difference between the answers, and this difference justifies the increasing knowledge about the effects of noise on hearing for personnel who practice shooting (Table 2).

Table 2. Comparison of knowledge of exposed (n = 65) and non-exposed (n = 50) officers on the effects of noise

Answers	Exposed Group (n=65)		Non-exposed Group (n=50)	
	Absolute Frequency (n)	Relative Frequency (%)	Absolute Frequency (n)	Relative Frequency (%)
Hearing loss	51	78.46	26	52.00
Stress	10	15.38	13	26.00
Headache	4	6.15	5	10.00
Earache	4	6.15	2	4.00
Sleep changes	1	1.53	5	10.00
Depression	1	1.53	0	0.00
Malaise/ dizziness	1	1.53	0	0.00
Don't know/don't know how to respond	8	12.30	14	28.00
No problem caused	1	1.53	0	0.00

Table 3. Complaints of auditory and extra-auditory symptoms reported by the exposed (n = 65) and non-exposed (n = 50) groups.

Symptoms	Exposed Group (n=65)		Non-exposed Group (n=50)	
	Absolute Frequency (n)	Relative Frequency (%)	Absolute Frequency (n)	Relative Frequency (%)
<i>Auditory</i>				
Tinnitus	10	15.30	9	18.00
Muffled hearing	9	13.80	3	6.00
Difficulty hearing	7	10.70	2	4.00
Dizziness	4	6.15	4	8.00
Otalgia	3	4.60	1	2.00
<i>Extra-Auditory</i>				
Headache	13	20.00	1	2.00
Stress/Irritation	10	15.30	6	12.00
Gastric problem	9	13.80	8	16.00
Sleep problem	8	12.30	5	10.00
Muscle pain	4	6.15	4	8.00
Hypertension	3	4.60	1	2.00
Lack of concentration	2	3.07	2	4.00
Cholesterol	2	3.07	3	6.00

Table 4. Auditory and extra-auditory complaints and symptoms stated by police shortly after shooting practice (n = 65)

Symptom	Absolute Freq. (n)	Relative Freq. (%)
No symptoms	42	64.60
Tinnitus	15	23.00
Temporary hearing loss	5	7.60
Headache	2	3.07
Irritation	2	3.07
Ear already cleared	1	1.53

As for auditory and extra-auditory symptoms commonly perceived by both the BOPE and administrative groups, no significant differences were observed between groups with respect to symptoms and complaints (Table 3).

The most frequently reported auditory complaints were tinnitus and hearing difficulty, in quiet areas, as reported by personnel exposed to noise in this study [17-19].

Shortly after shooting practice, BOPE members reported symptoms and complaints. As shown in Table 4, the most frequent symptom was tinnitus, followed by temporary hearing loss.

As seen, most of the exposed group claims touse hearing protection in all shooting practice (92.6%). If this result suggests efficiency in hearing protection, then there should not be hearing complaints after shooting practice (23%). It is known that the attenuation of a hearing protector depends not only on its physical characteristics, but also the person who uses it. Intermittent and inefficient use drastically reduces its effectiveness [20]. This statement agrees with a study of British soldiers which found that although all had knowledge about the effects of noise on hearing and the use of hearing protectors being the most used method to avoid these effects, many did not use it properly because they felt difficulties in communication, discomfort and an inability to use them in certain circumstances [21].

The knowledge that police officers have about hearing health preservation is superficial, and it necessary to have an appropriate education program to raise awareness of hearing care.

3) Auditory Profile of Police Officers

For the hearing profile, the officers underwent pure tone audiometry (InteracousticsAD229b Audiometer) held in a soundproof booth (TDH39P headphones) at frequencies of 250 to 8000 Hz bilaterally and when necessary, bone conduction (B71bone vibrator) at 500 to 4000 Hz. Sensorineural hearing loss was considered for thresholds above 25 dB HL [22].

For transient evoked and distortion product otoacoustic emissions testing we used the Interacoustics Eclipse equipment. In transient evoked OAE (TEOAE) we adopted a pass/ fail criterion, presenting up to 1000 stimuli in the form of a click in each ear, at 75dB SPL, with a maximum noise level of 45dBSPL. As criteria for TEOAE, the algorithm for 3dB-bandwidth method was used in which reproducibility must be greater than 75% in at least 3 consecutive frequency bands with signal/ noise level minimum of 3dB. As for the distortion product otoacoustic emissions (DPOAE), the extended DP-gram method was used. The standard used

for the examination was an intensity of L1-L2=10dB, with L1=65dB and L2=55dB; the f1/f2 ratio = 1.22. The test lasted a maximum of 90 seconds. Frequencies used: F1: 819, 1639, 2459, 3278, 4918, 6557 Hz and f2: 1000, 2000, 3000, 4000, 6000 and 8000 Hz. Distortion product was analyzed for frequencies of 638, 1278, 1918, 2556, 3836 and 5114Hz. The frequency of 500 Hz was not tested due to the level of noise present in the room that could mask the results. Distortion product otoacoustic emissions were considered present when they presented an amplitude greater than -10dB and with a signal/ noise difference greater than or equal to 6 dB.

The police in BOPE (exposed group), for analysis of the influence of service time on hearing, were divided into one group with service time of less than 15 years and another with longer than 15 years (Figures 3 and 4).

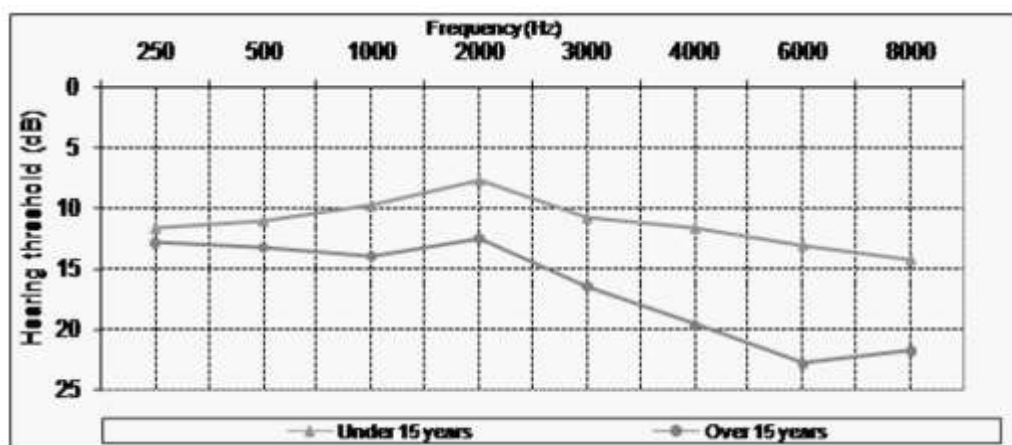


Figure 3. Comparison between the mean thresholds of the groups under 15 years and 15 or more years of service time - right-ear.

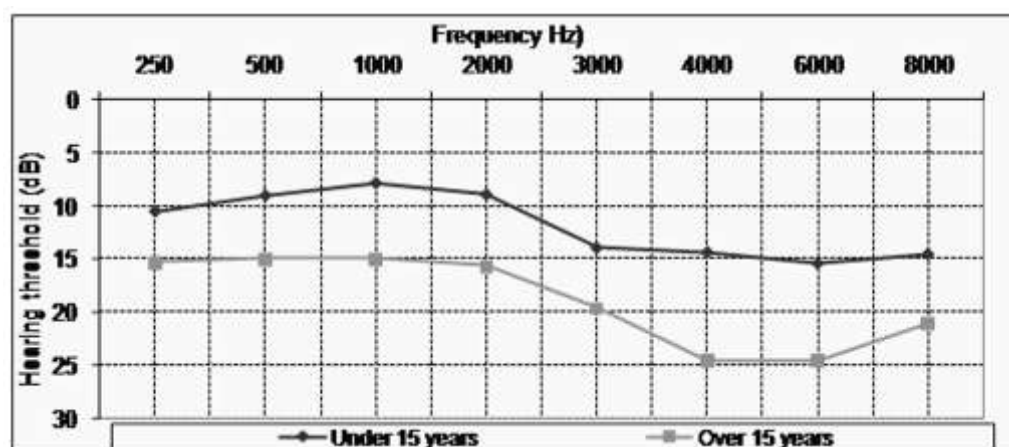


Figure 4. Comparison between the mean thresholds of the groups under 15 years and 15 or more years of service time - left ear.

The results indicated significant differences in the frequencies of 1, 2, 4 and 6 kHz bilaterally, between police exposed to noise in relation to length of service. The group with less than 15 years of service had mean pure tone thresholds that were better than the group with longer service. These data agree with the literature that the longer the exposure to noise, the greater the chances of developing hearing loss [9,15,19,23]. In the United States, for example, 40-50% of military personnel with over 10 years of service develop hearing loss due to noise and about 20-30% of the military with over two years of service already have some type of hearing impairment [24]. An Australian study also found that 40% of military respondents with more than 10 years of service had hearing loss suggestive of NIHL [14].

Excluding the age factor when comparing the results of all audiometric tests between the exposed and the non-exposed groups, we find the results shown in Table 5.

To characterize the impact of firearms noise exposure on hearing, excluded from the analysis were policemen with no hearing impairment suggestive of NIHL, i.e., not presenting an acoustic notch at 3000 Hz, and/ or 4,000, and/ or 6,000 Hz (nine subjects from both exposed and non-exposed groups).

The results in Table 6 characterize the auditory profile of the policemen who are exposed to fire arms noise. The differences between exposed and non-exposed groups are also shown in many previous studies with military personnel [14,25-27].

Testing of Transient Evoked Otoacoustic Emissions was calculated as a percentage of presence and absence, and the difference between the exposed and non-exposed group. Figure 5 shows the higher percentage of TEOAE absence in the exposed group (58.92%), while the non-exposed group shows higher presence of TEOAE (54.16%).

Among the officers exposed to noise, 14 of them showed symptoms suggestive of NIHL in the audiogram, of these, 78.5% had bilateral TEOAE absence, 7.2% with absence on the right and 14.3% with absence on the left.

Table 5. Classification of audiograms for Exposed and Non-Exposed Groups to firearms noise, according to NR7 Annex I (N = 115)

Audiogram classification (NR7)	Exposed Group (n=65)	Non-Exposed Group (n=50)
Within acceptable limits	64.61% (42)	96% (48)
Suggestive of NIHL	21.5% (14)	0% (0)
Not suggestive of NIHL	13.8% (9)	4% (2)

Table 6. Audiograms for Exposed and Non-Exposed Groups to firearms noise, excluding cases not suggestive of NIHL (N = 104)

Audiogram classification (NR7)	Exposed Group (n=56)	Non-Exposed Group (n=48)	p
Within acceptable limits	75% (42)	100%(48)	0.0001
Suggestive of NIHL	25% (14)	0%(0)	

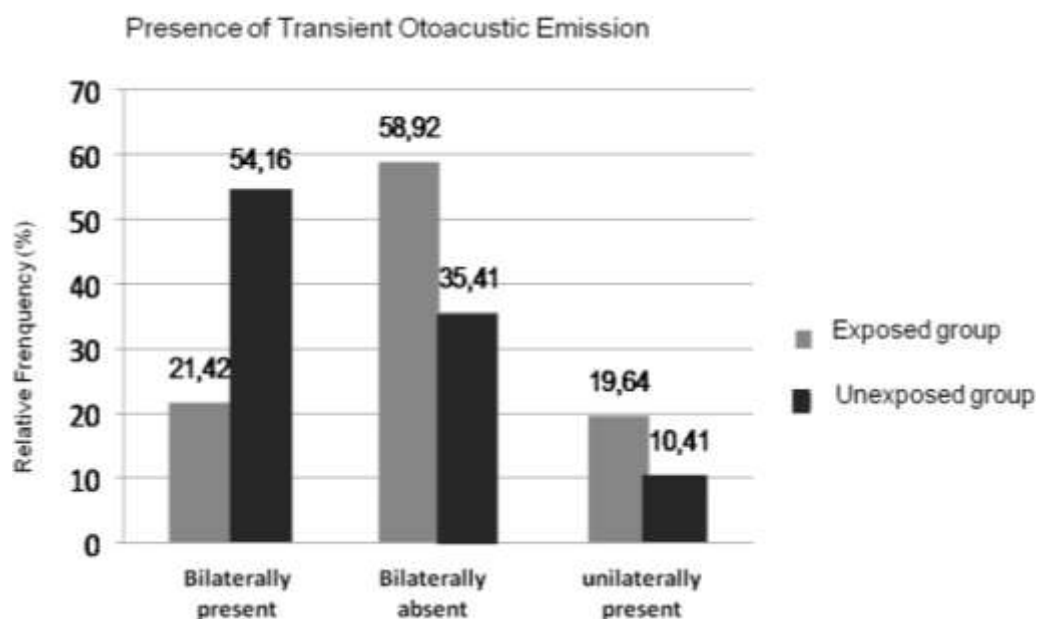


Figure 5. Comparison between the results of transient evoked otoacoustic emissions between the exposed and non-exposed groups (N = 104).

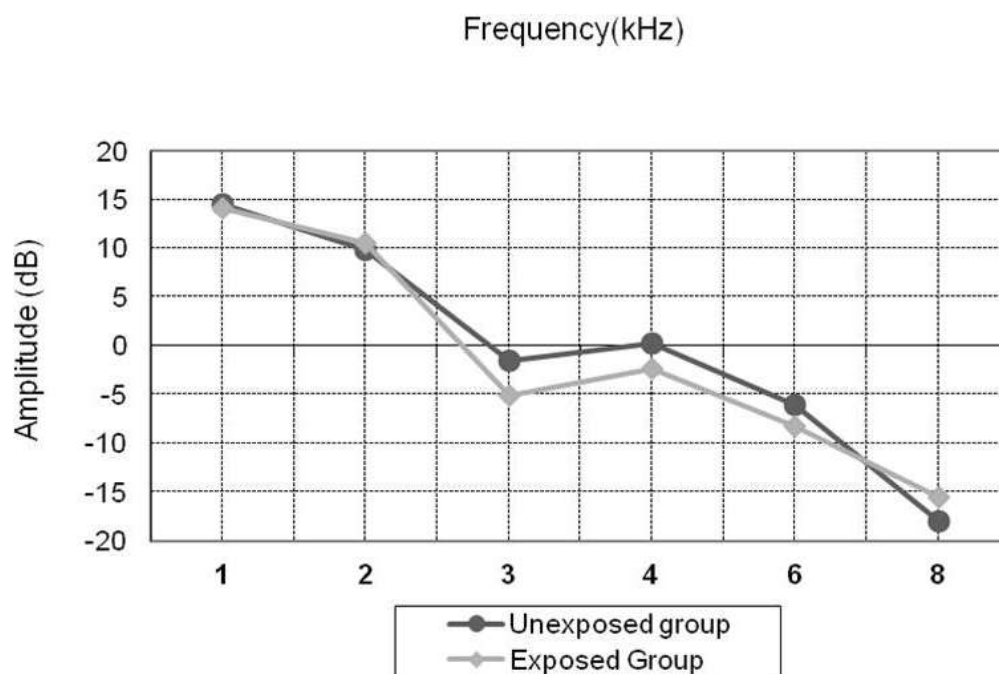


Figure 6. Comparison between the averages of DPOAE amplitudes of the right ear for frequencies, between Exposed Group (GE) and Non-Exposed Group (GNE) (N = 104).

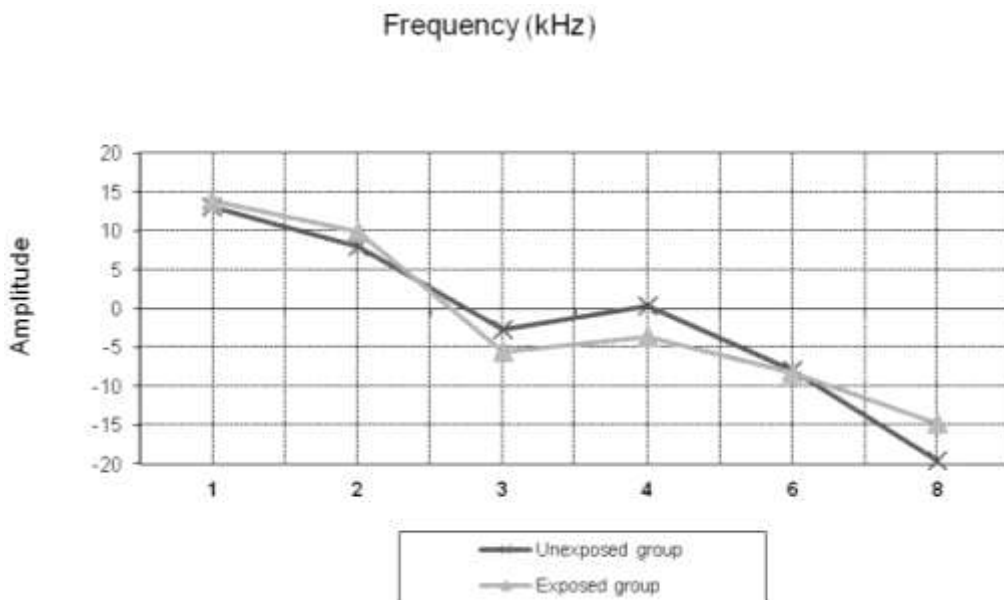


Figure 7. Comparison between the amplitudes of DPOAE, left, for frequencies between Exposed Group (GE) and Non-Exposed Group (GNE) (N = 104).

It was found that only 21.42% of the exposed group officers had bilaterally present TEOAE, while 54.16% of the non-exposed group showed bilateral TEOAE. This difference was significant, indicating that frequent exposure to impact noise may damage the outer hair cells. Other studies also indicate that there is a higher incidence of absent TEOAE among workers exposed to noise who present normal audiograms, showing that this is an effective test for early detection of cochlear hearing loss [10, 28-30].

Regarding the DPOAE, the response amplitudes in both groups were compared. Figures 6 and 7 illustrate the amplitudes in each ear from both groups. In them you can see that the frequencies of 3, 4 and 6 kHz decrease in amplitude between subjects in the exposed group.

With the results of TEOAE and DPOAE it is possible to say that these tests are of great importance and that only the most efficient audiometry detects early cochlear injury by firearms noise. Additional occupational audiology in the battery of tests for monitoring the hearing of workers exposed to noise would be a fast, objective and effective test for early detection of hearing loss induced by noise, making this test another important epidemiological surveillance tool in occupational health [10, 28, 30-32].

HEARING PRESERVATION FOR OFFICERS EXPOSED TO FIREARMS NOISE

From the characterization of risk, a Hearing Preservation Program can be planned and organized. The goal of the program is the reduction and/ or elimination of occupational hearing loss. The minimum recommendations for the implementation of a Hearing Preservation Program are to assess auditory risk, audiometric management, protection

measures, education, as well as individual and collective motivation, besides the evaluation of the program [20].

The program can be approached in three dimensions: the study and intervention in the work environment (risk identification); analysis of auditory profile and health of workers (audiometric monitoring); and educational activities [33]. Thus, through preventive measures, it is possible to maintain the hearing thresholds of military personnel and prevent worsening or onset of occupational hearing loss, thus preventing future harm not only to the health of individuals in the military, but the overall force in general.

The use of noise control measures, collective or individual, such as the use of hearing protectors in firing ranges, is not yet a common practice in the military. This is proven in the United States, where the first Hearing Preservation Programs started in the 70s. Since then, it has been demonstrated through regular audiometric testing, that the audiometry alone does not prevent hearing loss, but it does help to detect temporary or definitive hearing loss related to the use, or non-use, of hearing protectors. In military operations, both in training and in combat, the motivation to use hearing protection is very limited [15].

Studies in England have investigated about the knowledge of British soldiers on hearing preservation. The author noted that all the soldiers believed that hearing could be affected by exposure to noise in their work, but many were not aware of the presence of hearing conservation policies in the unit. A number of factors also prevented the proper use of hearing protection, despite being aware of its effectiveness. The military personnel cited communication difficulties, discomfort, and the inability to use protection in certain circumstances. The author of the study concluded that an effective Public Hearing Loss Prevention Program in the Army should incorporate appropriate knowledge, sociological issues, and economic considerations [21].

Noise exposure in the military profession is associated with armed conflict, which is highly detrimental exposure, because the noise sources are not predictable and the military are afraid that hearing protection can endanger safety by reducing locating signals and distorting communication [16].

The Committee on Noise-Induced Hearing Loss and Tinnitus Associated with Military Service in the U.S. states that Hearing Preservation Programs in the military environment are not fully adequate in preventing hearing loss in the military. And for better assessment, yearly monitoring is required not only for military personnel exposed to noise, but also for the implemented programs themselves [15]. So, like Hearing Preservation Programs, audiological services remain an important and growing need in the military.

Based on these data, we propose some steps to implement a Hearing Preservation Program in the Special Operations Battalion of the Military Police, with the aim of preserving hearing, as well as stabilizing and preventing occupational hearing loss:

- 1) Evaluation of the military work environment. Not only the shooting range, but also the places where there is normally exposure to noise, like cars, traffic, events, and emergencies.
- 2) Health assessments for military personnel that include periodic general health examinations like hearing tests and psychological evaluations.
- 3) Annual auditory monitoring of personnel exposed to noise, including otoacoustic emissions testing, in order to detect any worsening of the hearing.

- 4) Activities in the environment for noise control, such as sound insulation where there is a possibility, use of silencers on weapons, security warnings in risk areas, as well as studies on hearing protection appropriate for military action.
- 5) Direct involvement with the military personnel through educational activities, especially regarding awareness, not only about the use of hearing protection, but also on the importance of maintaining hearing health. For the population studied, it was noted that there is little expert guidance on the use of hearing protection, and what little guidance is provided is not standardized for quality control for which brands, models and attenuation levels are best.

To fulfill these steps, it is necessary that the institution incorporate, into its routine, the presence of specialized professionals (audiologists) that will maintain the program effectively.

Thus, through the characterization, monitoring and guidance of this population exposed to impact noise, it is possible to assist in its hearing preservation.

The proposal of a Hearing Preservation Program emphasizes the importance of training on the use of hearing protection and the need to educate military personnel about the importance of preserving hearing health for their professional and personal lives.

CONCLUSION

We found that the majority of military personnel exposed to high intensity noise show hearing loss and other symptoms like stress and headaches. Most personnel know that the best way to protect their hearing from impact noise is through the use of hearing protection. However, the protection offered by the force has no make, model or standardized level of attenuation, with the choice to use it or not being left to the discretion of the military personnel themselves. Also it was noted that there is little guidance on the use of these protectors. And the most common complaint among the group is the presence of tinnitus.

A quarter of the officers whose work exposes them to firearm noise, have audiograms suggestive of NIHL. The OAE testing proved its effectiveness in the early detection of hearing loss caused by impact noise exposure, and in the hearing monitoring of these subjects it was shown that most of the exposed personnel had TEOAE that were absent and with smaller amplitudes in DPOAE.

There is a need for monitoring and starting a program with educational activities aimed at preserving the hearing health of this group.

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Chapter 6

HEARING HEALTH AND STRESS FOR MILITARY POLICE

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ABSTRACT

Nowadays it is necessary for military personnel to have good hearing, mental and general health in order to enter military service. To this end, not only are hearing evaluations such as audiometric tests required, but also qualitative assessments on quality of life, which verifies the subject's emotional health and stress levels. This chapter will present theoretical concepts about the quality of life at work focusing on stress caused by military activity. The studies conclude the need to give more attention to the quality of life in military work, because it is not only exposure to noise that causes hearing loss and social stress, but also the nature of the profession itself that is stressful and often degrades the performance of military police.

INTRODUCTION

The proposal for quality of life at work is the improvement of conditions of work environments and technologies, according to the International Labor Organization. It is considered, from this perspective, the organization of work, understood as the division of tasks that determine away to produce and the division of workers into hierarchies involving relationships between operators and supervisors. The work environment involves, in addition to wages, the risk of accidents and disease, the technologies used to produce, the degree of autonomy and creativity of the worker, and the degree of worker control over the work process, which all influence health.

For the World Health Organization (WHO, 1995), quality of life is “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”[1].

Regarding the discussion on Quality of Work Life (QWL), it had its beginning in the 70s, when there were struggles from workers and students against the Taylorist/ Fordist production systems.

At first, QWL was understood only as job satisfaction, which only refers to working conditions and remuneration received, thus being an individual reaction to a job. Later the term took into account more cooperative projects, which although seeking to provide greater worker satisfaction, was still associated with increased worker productivity.

Currently, the concern with QWL focuses on the search for humanization at work, changing it and adapting it to allow greater worker satisfaction and greater organizational productivity, considering key elements for solving problems, the restructuring of the basic nature of work, innovation in compensation and the rewards system, and improving the work environment.

Therefore, quality of work life is related, currently, to a way of thinking that involves humans, their work and its organization, focused on the welfare of workers in the workplace along with organizational effectiveness [3, 11].

However, there are several factors that can decrease the quality of life, such as the emergence of various illnesses, including stress.

Several studies have shown that stress is one of the factors most responsible for excessive tardiness and absences at work, as well as for medical leave, relationship problems with superiors, subordinates, colleagues and customers, decreased productivity, lack of creativity and originality in ideas, and even depression, alcoholism, smoking, and drug use.

Stress is the new challenge of this century and is directly related to the ability of an individual to bear a particular responsibility, for a time, uninterruptedly, while being under some kind of psychological pressure. Preventing psychological stress becomes a challenge as the subjectivity of the problem does not accurately allow a determination of what the triggers are, and, therefore, how to avoid it. However, one should not only focus on the emotional reasons for stress. Workplaces that have thermal and/ or acoustic discomfort; long hours without interruption; physical, sensory or postural stress can also be considered stressors [2].

OCCUPATIONAL STRESS

One of the most common characteristics of the organization of contemporary societies is stress, which although originally constitutes a natural reaction of adaptation of the human body, has assumed the status of a disease. This is probably due to the fact that the performance requirements of roles and tasks are beyond the adaptive capacity of the individual.

The same happens today in relation to the working environment into which the individual is inserted, generating what we call occupational stress, which can be caused not only by issues relating to the work itself, but also, and perhaps mainly, by organizational characteristics at work. These are events, situations, or contingencies to which the worker is subjected that may exceed their threshold of tolerance to pressure and put the worker in a vulnerable situation, depending on the psychophysical structure of each person.

Occupational stress has been investigated to be present in most organizational environments. The stress in this case may be due to an inability of the individual to cope with

the stressor present in work contexts, commonly causing mental and/ or physical illnesses, which can in turn cause damage [5].

Gradually, there has also been an increase in studies on stress in professions involving risk of life, and, at the same time, are critical to the orderly operation of society, as in the case of military and civil police officers and firefighters.

The military police force is a complex organization with groups of interests that are resistant to change. Reflections on the health of police work in Brazil are still quite limited, and this is because the military dictatorship silenced these issues for a long time, and those policies still echo today. For this reason, in the context of the state military police forces, one must consider both the aspects of work organization as well as the risk situations to which these professionals are exposed, especially considering the significant increase in violence and lack of jobs [6].

In this context, it was exactly the significant increase in violence that put the performance of the civil and military police into the spotlight. However, it can be observed in Brazil that there is a significant distrust of the police, unlike what can be seen in countries such as Germany and the United States. This fact may result from constant accusations of corruption and excessive police violence, as well as the ignorance of the public about domestic politics, culture, and other issues relating to these institutions. This ignorance has prevented society from perceiving the dissatisfaction that the police themselves have with various aspects of their work. One source that contributes most to the controversial image of the police officer is provided by the media, which now puts officers in the position of the hero, showing their actions in combating crime, but sometimes in the position of villains who are corrupt or kill innocent people. Perhaps society is unaware of police work, whose function is to contain violence, but at the same time running the risk of reproducing violence or being its victim [5].

Besides being a life-threatening activity, the characteristics of the military police organization, including its structure, hierarchy, discipline and rules of conduct, which can be, in many cases, also considered stressors, as they impose severe restrictions on expression and personal development of the police officers, with low pay as a significant factor of general dissatisfaction among the officers.

One of the characteristics of the military profession is to live with risk, either in training, in daily life, or at war, and that comes across in every day with very adverse situations requiring rapid solutions, intervening in situations with human problems full of conflict and tension. These professionals are also subjected to strict principles of hierarchy and discipline, absolute dedication, continuous availability, physical force and constant professional improvement. Even when inactive, officers must remain bound to their profession and ready to serve if called up with an eventual return to active service, even when paid as a reservist; plus they have restrictions regarding labor rights [6].

Moreover, the risk to which they are exposed, which creates uncertainty and tension, not only accompanies the police at the time and place of work, but also outside of it, since they are recognized by their uniforms [7].

Studies on the health of civil and military police in the state of Rio de Janeiro affirm that the police, as workers, are underserved with health issues, and this has deep historical roots, which intensified with the military dictatorship in Brazil. The field of occupational health cannot omit consideration of jobs in public safety, a segment which is one of the most vulnerable to accidents and death at work [8].

Another important factor relates to the fact that in a male-dominated work place, we must consider that illness, stress or distress may be associated with male weakness, causing the police officers to hide these issues from colleagues, thereby not seeking necessary treatment in order to defend himself against negative labels [5].

However, contradicting this situation, a study of Brazilian military police in the state of Paraíba revealed that between 2003 and 2005 there was an average of 489 police officers away on sick leave [6].

STUDIES ON STRESS IN THE MILITARY POLICE IN BRAZIL

The military profession is a high risk activity because these professionals deal with violence, brutality and death in their daily lives, being among the professionals who often suffer from stress, not only due to the characteristics of their work but also because of the pressure society puts on them demanding their competence and commitment. One study investigated the occurrence and stages of stress among 264 military police, obtaining as a result that 47.4% of the police had symptoms of stress. Psychological symptoms were recorded in 76.0% of the police with stress, and physical symptoms in 24.0%, with women being more affected than men. Although the conclusion was that the levels of stress and symptoms do not indicate a critical situation of fatigue, it recommended preventative action by the police organization, which could include the implementation of a program of diagnosis, counseling, and stress management [9].

A survey of 50 members of the Military Police in Brazil found that 38% of police officers had symptoms of stress, with no significant difference between police officers who perform administrative duties and officers who have duties that take them to the streets [10].

Another study diagnosed the quality of life at work and occupational stress in 1,152 military police officers in the state of Minas Gerais. Although the study revealed a high level of satisfaction with the military police work itself, there was a significant level of dissatisfaction with aspects of the culture and organizational structure of the military police, which, along with dissatisfaction with pay, constituted the main sources of active pressure on the military and caused high levels of stress, stemming from a high level of dissatisfaction with the institution.

A series of recommendations arising from the findings, which include rethinking the organization of work, possibility of expression and autonomy, recovering self-esteem, the image of the police in society, and also the realization of a program for jobs and wages that reduce or eliminate the need to moonlight [11].

Studies have also addressed the issue of gender in the military police. In a predominantly male work environment, being a woman is a powerful trigger of stress. One of the most important findings is that the presence of women does not have a gender perspective and real understanding of differences, which eliminates existing inequalities in the force, both for officers as well as precincts, regarding health or operational units [12, 13].

In 2009 a detailed survey of the literature about police work and its implications for mental health was conducted and found that, despite the significant increase in scientific production since 2000, the results are inadequate when compared with the relevance of the topic. The author justifies this as being probably due to the difficulty of gathering qualitative

data within the police force due to issues of hierarchy and protocols relevant to the organization as an institution. For the author, qualitative studies could lead us to consider the police officers in a subjective manner, giving voice to these players and bringing up issues that would hardly be captured by quantitative studies, although these studies are also unquestionably valuable [7].

In 2010, a study was conducted with 75 police officers from Santa Maria, divided into three groups: 26 officers working in the emergency-call operations center, 7 officers working in administrative areas, and 42 in patrolling activities. As a result, a significant presence of stress levels in the emergency-call center and patrolling sector was found, totaling more than half of the participants surveyed. The most common stress symptoms found were a feeling of physical exhaustion, fatigue, muscle tension, memory problems, insomnia, irritability, excessive emotional sensitivity, and constantly thinking on one subject. The authors warn that such symptoms are worrisome because they can impair the performance of the activities developed by the military police, generating losses for society [13].

FINAL CONSIDERATIONS

It can be seen that working as a policeman is a stressful activity, and that this characteristic is perhaps necessary in the working of an effective officer. On the other hand, the high level of stress may end up damaging the health of the officers.

There is a need for larger studies made with the aim not only of characterizing the level of stress, but also proposing improvements in the quality of life for military police officers, starting with an awareness of the risks involved to educational measures and other approaches that preserve the health of these professionals.

The development of preventive programs for police officers should include: investigations into health conditions with a focus on epidemiological methods; healthcare planning, in seeking solutions with an emphasis on health promotion, using intervention activities not only for officers, but also for the workplace; an evaluation program developed as part of the planning, forecasting and provision of solutions for managing the implementation for improving health conditions.

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Chapter 7

EFFECTIVENESS OF HEARING PROTECTION DEVICES (HPD) IN ACTIVITIES WITH FIREARMS

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ABSTRACT

Hearing protection devices have the function of protecting the hearing against potential risks in environments that may threaten safety and health as a result of exposure to loud noise. This measure is used when it is unfeasible to adopt collective protection or until it is effectively implemented. The hearing protector is still the main instrument of hearing loss prevention in all fields of work where there is noise. This is no different in the military population. We present in this chapter a survey covering different aspects of one type of hearing protection (attenuation and comfort) provided for some aspiring officers of the Military Police.

INTRODUCTION

Exposure to intense sound pressure levels (SPL) can be minimized with the use of Hearing Protection Devices HPD to protect hearing. The choice of the type and model of PPE, as well as training for its proper use are aspects that deserve attention from health professionals [1, 2, 3].

The use of hearing protection involves many aspects that must be considered in order to obtain an efficient use in reducing the noise that reaches the inner ear. Among these aspects should be considered: noise attenuation and noise leakage, comfort, proper placement, as well as care and maintenance of hearing protectors.

The estimation of noise attenuation by HPD has been studied by several authors. The methods used in laboratories (well-controlled laboratory conditions - ANSI S3.19 (ANSI, 1974) or ISO 4869-1 (ISO, 1990) are criticized for not representing realistic situations for their use. Even when not using an artificial head in the tests, as with the protocols for estimating noise attenuation using the REAT (real-ear-attenuation-at-threshold) method -

based on ISO 4869-1/90, ANSI S3.19-1974 ANSI S12.6-1984 and ANSI S12.6-1997 - A and B), critics point to the great variability that can occur between the test subjects and real users. These differences relate to the small number of samples for the generalization performed and the threshold comparison, of the test subjects and those who will actually use the HPD.

The literature in this area has shown that the attenuation data obtained in laboratories and used by hearing protector manufacturers are smaller than those evaluated in real situations among users. This is because the correct placement of HPD is a factor that interferes with noise attenuation [4].

In an attempt to minimize these criticisms, estimated attenuation using the microphone-in-real-ear (MIRE) method has been employed by some researchers. This method uses two microphones: one miniature microphone inside the HPD, placed in the ear canal of the subject, which captures the attenuated sound that reaches the ear, and another external microphone outside the ear, which captures the ambient sound.

The ideal noise attenuation will be analyzed for each situation, it is expected that the hearing be protected, but without the individual losing contact with the surrounding environment. The way attenuation is expressed, and the method used, either by frequency bands in decibels or by a global attenuation value such as: the Noise Reduction Rating - NRR or Noise Reduction Rating Subject-Fit - NRRsf, to be considered for choice of HPD.

However, it is important to consider that noise can reach the inner ear by bone and human tissue transmission, by the vibration of the ear itself, noise transmission through the material of the HPD, and leakage due to inadequate contact between the ear protector and the user's body, which depends on proper training regarding the placement of HPD [5].

So, in addition to noise reduction, other aspects are important in choosing the most appropriate HPD for each activity, as they relate to ease of use. These aspects of the HPD are: its weight, the pressure it puts on the ear, its texture, its ability to dissipate heat generated, its ability to absorb perspiration, its interference in achieving the activity, its interference in verbal communication, and the way it is placed on/ in the ear [6].

The variety of HPD available on the market has grown significantly in the last 40 years [1, 7, 8]. Selecting the correct device for each situation is important. Attenuation may not even be the most important criterion to be considered, for some authors, as what must also be considered is comfort, the need for communication, appropriate use, cost, durability, and even its suitability for the activity being practiced by the user [2]. For the hearing protectors to actually be used, it is necessary that they be comfortable [5].

This chapter aims to analyze some HPD for the users of firearms, and their different characteristics, such as attenuation and comfort.

TYPES OF HPD FOR EXPOSURE TO FIREARMS NOISE

Hearing protection against the SPL produced by firearms, considered to be impact noise, has peculiarities in relation to protection against continuous noise, typical of industrial activities.

The noise reduction rating (NRR) required for HPD used for firearms noise must be higher than for PPE used for continuous noise, for use in industries. Moreover, in many situations, the user of a firearm needs to be able to communicate for safety reasons. Among

these are mostly professionals who are using firearms daily for occupational reasons, such as the police and military.

To adapt to these hearing protection needs, there have been a few attempts over the years to produce HPD specifically for firearms users. The first HPD for protection from firearms noise was designed in the First World War. Mallock, in 1914, in England, designed an ear plug type for use by the military in the war [9]. And Tod, in 1914, based on the idea of the diaphragm, developed a hearing protector placed over the ear with a damper that closed in the presence of impact noise for use in exposure to firearms. Still in 1914, Kalse and Kalse adapted a manual phone-type device in an earmuff protector, which had non-linear noise attenuation properties for shooters [10].

Described below are some of the types of headphones available on the market today designed to protect users' hearing from firearms noise:

1) Passive Hearing Protection:

In this group are HPD with mechanical noise attenuation, without any electronic device that regulates the attenuation for frequency or sound pressure level. They can be:

1.1) Earmuffs:

This type of hearing protection is designed to fully enclose the ear. Some models of this type are suitable for ear protection when using firearms with high levels of noise attenuation, between 21 and 25 dB (NRR) according to the manufacturers;

1.2) Earplugs:

Frequency dependent: nonlinear, with small holes creating an acoustic filter that allows the passage of low-frequency sounds and more attenuation for high and medium frequencies, which enables improved verbal communication awareness. NRR 20-22 dB;

1.3) Earplugs with filters:

Dependent on sound intensity (variable attenuation) using filters of different sizes and materials; adjustable to the different needs for noise attenuation, with some models incorporating a valve that lets you manually adjust the attenuation level. The NRR increases with the increase of intensity (12 to 22 dB);

2) Electronic Hearing Protection:

These include electronic devices that enable attenuation dependent on sound pressure levels. Running on batteries, they are designed to increase speech sounds, but reduce impact noise to a safe level, recommended for shooting activities for both sport shooting and police activities. Some types allow reception of communication through the device.

2.1) *Electronic earplugs*: come in various models such as: custom, open ear, or with headset for communication. Attenuate ambient noise and cancel out peaks of impact noise. There is great variation in NRR depending on the model and brand.

2.2) *Electronic earmuffs*: control the sound pressure level, mitigate noise impact immediately, with NRR around 19-20 dB.

- 2.3) *Electronics earmuffs with transmission dependent on sound pressure level:* contain a microphone and an amplification system that transmit external noise to headphones placed inside the earmuffs. This system was designed to amplify only certain areas of the sound spectrum. The amplification system has adjustable maximum sound pressure inside the device and a cutout level, at which the electronic system shuts down. NRR around 21-26 dB
- 2.4) *Electronics earmuffs with communicators:* enable communication between wearers of hearing protectors by having microphones transmit and receive speech sounds. NRR of 20 dB.

PARAMETERS OF COMFORT FOR MILITARY HPD

The proper use of hearing protection is a challenge for hearing loss prevention. Lack of knowledge about the risk of exposure to noise and the lack of guidance on how to properly use HPD are mentioned as factors that discourage use. Among the reasons for not using hearing protection adequately is discomfort, as well as difficulties in communicating and hearing environmental sounds important for safety. In addition to the difficulties in choosing HPD, having guidelines regarding use of these devices is a concern [11]. The effectiveness of a hearing protector is not only measured in noise attenuation, but also in the way it is used. For this reason, it is essential that military personnel understand the risks and understand the need for using HPD. This understanding can ensure the right to request the proper HPD that is specific to certain activities [12].

Thinking about these issues, we developed a study that aimed to understand the perception of military police who practice shooting every week on the important aspects in relation to HPD and an evaluation on the comfort of earplugs. The selected group was part of the training course for officers in the Military Police of Paraná - Brazil who had no prior experience with using the earplugs used in the research. The work proceeded in three steps:

- 1st) guidelines to the subjects about the risks of exposure to firearms and training on the proper use of the hearing protection used in the study, conducted at the Military Police Battalion HQ;
- 2nd) identification of aspects considered important for the police in relation to HPD;
- 3rd) review of the aspects of comfort in using an earplug with a noise filter.

The study included 19 police officers, all male, with a mean age of 24.8 (minimum 19, maximum 34, standard deviation/ SD = 4.48 years), most (14) with high school diplomas and (5) with college degrees. Among the officers, three had noise induced hearing loss (NIHL) with an acoustic notch.

The earplug used in the study was the 3M COMBAT ARMS® model, a pre-molded insert type, which is a device that changes the noise reduction to the situation of exposure to impact noise from the shot (Open or Shot mode: the sound moves to the ear through a special filter that allows the passage of low-frequency sounds, but attenuates high frequency sounds, or, the more intense the impulse noise, the more limited the noise will be; and Closed or Constant Protection mode: that attenuates continuous noise mainly from high frequency sound (such as

engine and ambient noise), allowing the military to carry out operations without removing the earplugs. Thus, there are two attenuation types: Open or Shooting mode with a NRR of 7 dB and the Closed or Continuous Protection mode with a NRR of 23 dB (ANSI S3.19-1974).

In 2006, the proposed instrument was used in a survey consisting of two questionnaires [13]: the Evaluation of Comfort Parameters (Appendix 1), which evaluates the relevance of the comfort parameters for hearing protectors, and the Assessment of Hearing Protectors (Appendix 2), to evaluate the comfort in the use of earplugs (a). The instrument uses a Likert scale, with Questionnaire 1 (Appendix 1) covering issues on a scale of 1 to 5, with 1 being *Insignificant* and 5 being *Very Important*, and Questionnaire 2 (Appendix 2) applied after 30 days experience with earplugs (a), allows the classification of hearing protectors used by the subjects associated on a scale of 1 to 5, where 1 is the *Most Favorable* and 5 the *Least Favorable* situation.

The following are the results of the questionnaires:

Table 1. Average scores on the questionnaire on aspects considered important by officers for hearing protection (N = 19)

Points	Attenuation	Pressure	Weight	Texture	Heat	Sweat	Do tasks	Insertion	Communication
Average	4.8	4.4	3.7	3.6	4.1	3.8	4.5	4.4	4.6
Std Dev.	0.40	0.81	1.10	0.92	0.70	1.08	0.93	0.81	0.67

1= insignificant / 5=very important

Observe that all questions were assessed as significant (all had scores above 2.5, which is considered to be “normal”), however, the question for “attenuation” was considered the most significant aspect in the perception of the police, with texture and weight being less significant.

The officers’ evaluation of the COMBAT ARMS® hearing protectors is in the table below.

Questions regarding pressure in the ear (2.7) and difficulty in performing tasks (2.7) had averages above 2.5 (considered normal), but the remaining questions scored higher.

In relation to the overall comfort in the ear, the average score was 3.1 (SD = 1.36) showing the earplug to be comfortable.

EVALUATION OF ATTENUATION EARMUFF TYPE PROTECTOR USED BY MILITARY

The study with the group of 19 police officers, with the objective of evaluating the effectiveness of hearing protection in shooting practice by the military police, was continued

to review the attenuation of an earmuff-type device during practice shooting for the military Police Battalion in Curitiba - Brazil.

The PELTOR H10A® earmuff-type protector, made by 3M Brazil, has attenuation indicated by the manufacturer for a NRR of 30 dB and 27 dB of NRR(SF).

Table 2. Evaluation of the police regarding the earplugs (N=19).

Points	Attenuation	Pressure	Weight	Texture	Heat	Sweat	Do tasks	Insertion	Communication
Average	1.8	2.7	1	2.4	1.3	1.7	2.7	2	1.6
Std Dev.	0.94	1.44	0.00	1.18	0.82	1.03	1.49	1.56	0.83

1=most favorable / 5=least favorable.

We conducted the evaluation of sound pressure levels at an outdoor firing range for shooting practice for the military police with a Taurus® .40 pistol and with a 12 gauge shotgun firing slugs, both weapons were loaded with CBC (*Companhia Brasileira de Cartuchos*) brand cartridges. We used the MIRE method, and the measurement was performed using a Svantek (Poland) model SV 102 sound level meter, with programming for channel 3 using the following weights: (1) A/ “slow”; (2) C/ “impulse” and (3) C/ “fast”. The peak measuring range was between 60 and 146 dB. The sound level meter was attached to the belt of the subject with a microphone on the collar of his shirt. Before each measurement, the microphones were calibrated by means of acoustic calibrator, model CR:514 by Cirrus Research plc.

The measurements were performed following Brazilian [14] and international [15] recommendations. The peak values and maximum limit (Lmax) were measured and the noise frequency spectrum (octave band) was analyzed.

According to Annex 2 (Limits for impulse noise) from Norm n.15 [14]:

1. Impulse noise shall mean that which presents acoustic energy peaks of less than one (1) second with intervals of longer than 1 (one) second.
2. Impulse levels should be evaluated in decibels (dB), with a sound pressure level meter operating in the linear circuit with circuit response set at impulse. The readings should be made near the ear of the worker. The tolerance limit for impulse noise will be 130 dB (linear). In between the peaks, the existing noise should be evaluated as continuous noise.
3. In case of unavailability of measuring the sound pressure level in using the impulse setting, it shall be valid to use the fast setting and “C” weighting. In this case, the tolerance limit will be 120 dB(C).
4. Activities or operations that expose workers without adequate protection, to impulse noise levels of greater than 140 dB (linear) measured at impulse response setting, or

greater than 130 dB(C) measured at the fast response setting, offer a serious and imminent risk.

By international standards, the International Institute of Noise Control Engineering provides 140 dB(C) as the limit of exposure to impulse noise [15].

Considering the above regulations, the police officers should not be exposed to values greater than 140 dB(C) peak, and the value of Lmax should not exceed 120 dB(C).

For data that will be presented in this chapter two series of shots (and instruction) were considered: for the .40 pistol, training was conducted for 35 minutes, and for the 12 gauge shotgun, the session lasted 19 minutes. The lines of fire consisted of 10 officers in each battery, each of whom fired 5 shots per series. There were four series of .40 pistol shots and two series for the 12 gauge shotgun.

The following are the results.

Table 3. Results of noise from the .40 pistol

Weapon / Pistol	Filter	Detector	Peak (dB)	Max (dB)	Leq (dB)
External Microphone	A	Slow	143.9	115.3	95.7
	C	Impulse	141.8	126.9	97.4
	C	Fast	141.8	122.4	97.4
MIRE	A	Slow	135.5	102.5	77.8
	C	Impulse	134.1	126.5	93.3
	C	Fast	134.1	123	93.3

Table 4. Results of noise from the 12 gauge shotgun

Weapon / Shotgun	Filter	Detector	Peak (dB)	Max (dB)	Leq (dB)
External Microphone	A	Slow	144.9	111.7	93
	C	Impulse	141.8	127.8	95.4
	C	Fast	141.8	123.1	95.4
MIRE	A	Slow	117.7	89.8	64.8
	C	Impulse	128.1	121	86.7
	C	Fast	128.1	117.2	86.7

Table 5. Results of the noise attenuation for the weapons used (MIRE)

Weapon	Microphone	125 Hz	250 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz	8000 Hz	Total A	Total C
.40 Pistol	External	68.3	78.1	88.6	92.2	89.5	84.8	81.7	95.7	97.4
	Internal	61.4	67.4	68.1	65.2	72.3	71	71.3	77.8	93.3
	Difference	6.9	10.7	20.5	27	17.2	13.8	10.4	17.9	4.1
12 gauge shotgun	External	70.2	79.3	85.7	89.8	85.9	81.9	78.8	93	95.4
	Internal	56	59.6	54.2	53.2	58.4	54.2	48.9	64.8	86.7
	Difference	14.2	19.7	31.5	36.6	27.5	27.7	29.9	28.2	8.7

Legend: Total A – results for average total of all A frequency measurements; Total C - results for average total of all C frequency measurements.

Table 6. Comparison of the results of attenuation found in comparison to the numbers from the earmuff-type manufacturer (values in dBA)

Octave Band (Hz)	125	250	500	1000	2000	4000	8000	Total A
Manufacturer	16	22.9	34	36.8	35.9	38	38.2	27
.40 Pistol	6.9	10.7	20.5	27	17.2	13.8	10.4	17.9
12 gauge shotgun	14.2	19.7	31.5	36.6	27.5	27.7	29.9	28.2

Legend: Total A – results for average total of all A frequency measurements.

From the presented results, it was identified that evaluated the earmuff protector was efficient for hearing protection for the officers, except in the “Lmax / fast” setting, where a value of 123 dB(C) was observed for the .40 pistol, so the measured values exceeded the limit recommended by NR-15 [14].

Possibly due to the differences in weapons, cartridges, distance from the wall, and, hence, the physical characteristics of noise, it was observed that the earmuff protector was rated most effective for noise attenuation for shotgun noise, relative to the noise of the pistol. While average attenuation for the shotgun stood at 28.2 dB(A) (above the 27 dB(A) described by the manufacturer), the attenuation of the noise from the pistol was 17.9 dB(A).

CONCLUSION

The theme of hearing protection for noise impulse is challenging and very current. There are several models and brands of hearing protection devices on the market, but often the attenuation values provided by the manufacturers are not proven by measurements taken in the field. The challenge for professionals working in this area increases when we see the need to associate good quality in noise attenuation with device comfort.

The above noise levels in training with the .40 pistol and 12 gauge shotgun are above those permitted by law, showing the need to use hearing protection during training.

For hearing protection to be used properly and all the times by the military, the main thing is comfort. And to assess the comfort of a hearing protector, it is necessary to have the opinion of its users [8]. This opinion, in this study, was shown in the questionnaire, in that the COMBAT ARMS® brand pre-molded earplug hearing protector has a medium level of comfort (3.1), and is therefore characterized as comfortable by users surveyed.

For choosing the best protector made for this population, we need to evaluate more protectors, not only for comfort, but also for attenuation. This type of analysis was performed with the PELTOR H10A® brand earmuff hearing protector, which was proven effective in noise reduction for the 12 gauge shotgun, however with regards to training with the .40 pistol, its performance was just “fair”. Therefore, other actions should be introduced to protect the hearing of the police officers.

The ideal would be to test both aspects of each of the hearing protectors available and then come to the conclusion for the most appropriate device for the population in question.

APPENDICES

Questionnaire 1. Evaluation of Comfort Parameters

Name:	
Job Title:	Sector:

(Note: this questionnaire is to know which topics are of the greatest importance to be evaluated in the short term and not specifically on the protector that is being tested. Remember that 1 is insignificant and 5 is very important.)

Rate, in your opinion, the relevance of each of the comfort parameters for Personal Protection Equipment for Hearing, the overall comfort of the protector, on a scale of 1 to 5, wherein:

Attenuation	Insignificant	1	2	3	4	5	Very Important
Pressure Dampers – done by rods – in ear canal	Insignificant	1	2	3	4	5	Very Important
Weight	Insignificant	1	2	3	4	5	Very Important
Texture	Insignificant	1	2	3	4	5	Very Important
Ability to dissipate generated heat	Insignificant	1	2	3	4	5	Very Important
Ability to absorb sweat	Insignificant	1	2	3	4	5	Very Important
Inconvenience when doing tasks	Insignificant	1	2	3	4	5	Very Important
Insertion	Insignificant	1	2	3	4	5	Very Important
Verbal Communication	Insignificant	1	2	3	4	5	Very Important

Questionnaire 2.- Evaluation of Personal Hearing Protector

Name:	
Job Title:	Job Title:

Rate the hearing protector used based on the topics that are shown below, on a scale of 1 to 5, for:

Attenuation	Good	1	2	3	4	5	Poor
Pressure Dampers – done by rods – in ear canal	Adequate	1	2	3	4	5	Inadequate
Weight	Light	1	2	3	4	5	Very Heavy
Texture	Soft	1	2	3	4	5	Rough
Ability to dissipate generated heat	Good	1	2	3	4	5	Poor
Ability to absorb sweat	Good	1	2	3	4	5	Poor
Inconvenience when doing tasks	None	1	2	3	4	5	High
Insertion	Easy	1	2	3	4	5	Difficult
Verbal Communication	Easy	1	2	3	4	5	Difficult

Overall, how would you classify the protector that was used?

Uncomfortable	1	2	3	4	5	Comfortable
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Chapter 8

HEARING IMPAIRMENT AFTER PERINATAL ASPHYXIA

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ABSTRACT

Perinatal asphyxia, i.e., hypoxia-ischemia occurring during perinatal period can damage both the cochlea and the neural and central auditory pathway in newborn infants. It has been considered to be one of the major risk factors for acquired auditory impairment in infants and children. In the last three decades, the immature auditory system in human infants has been assessed and monitored mainly using non-invasive neurophysiological techniques, typically auditory evoked potentials for functional integrity of the auditory pathway and otoacoustic emissions (OAEs) or distortion product otoacoustic emissions (DPOAEs) for cochlea function. These techniques have also been commonly used to study maturation of the auditory system and detect functional abnormalities or impairment of the system. Among these neurophysiological techniques, brainstem auditory evoked response (BAER) is the most widely used evoked potential to assess the developing auditory system and detect abnormality in clinical conditions that may affect the brainstem auditory pathway. This article reviews literatures for the effects of perinatal asphyxia on the immature peripheral hearing, and mainly discusses our findings obtained using the BAER and DPOAEs during the neonatal and postnatal periods in term infants after perinatal asphyxia. Particular attention is paid to the dynamic changes in BAER threshold during the first one month after perinatal asphyxia. The threshold is elevated significantly on day 1. The elevated threshold is then decreased progressively on days 3 and 5, continuously decreased more slowly on days 10 and 15, and returns to a near normal level in most infants on day 30. During the first month, the threshold elevation, suggesting hearing impairment, occurs in one-third of term infants after perinatal asphyxia. By the end of the first month, one in ten still has threshold elevation. Postnatal studies documented that with increasing age the impaired hearing tends to improve further. However, by 3 months after birth, the hearing impairment that exists in a small proportion of the infants after perinatal asphyxia is unlikely to show any

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further significant improvement, and is more likely to be persistent or permanent. These findings indicate that hearing impairment after perinatal asphyxia is mostly temporary, with only a few infants having persistent impairment. More recently, auditory neuropathy has attracted considerable interest. Whether perinatal asphyxia can cause auditory neuropathy in human infants remains to be determined, although early animal experiments suggested that hypoxia and hypoxia-ischemia in immature animals could cause auditory neuropathy. This is an interest area to be explored.

INTRODUCTION

In human infants there is a critical period for hearing development that extends from before birth to about possibly 3 months after birth (Jiang and Tierney, 1995). During this critical period of development, the peripheral auditory system is particularly susceptible to various unfavourable factors, including asphyxia (Fahnenstich et al., 1999; Mencher, et al. 1981; Newton, 2001; Norton, 2000a,b; Pujol et al., 1990; Uziel, 1985; Wilkinson and Jiang, 2006). Perinatal asphyxia, i.e., hypoxia-ischemia occurring during perinatal period, is considered to be one of the major risk factors for acquired hearing impairment in infants and children (Borg, 1997; Flint, 1983; Hecox and Cone 1981; Jiang, 1995,1998; Kountakis et al., 2002; Mencher and Mencher, 1999; Mencher, et al. 1981; Newton, 2001; Yasuhara et al., 1986). It is generally accepted that hearing impairment after perinatal asphyxia is more likely to be temporary than permanent (Borg, 1997; Jiang et al., 2004a). Only a small proportion of infants after perinatal asphyxia have a persistent or permanent hearing impairment (Jiang, 1995,1998; Sano et al., 2005).

Unlike in animal experiment, in human infants after perinatal asphyxia, hypoxic-ischaemic damage to the cochlea and neural pathway may not be the only cause of hearing impairment. Infants after perinatal asphyxia are often associated with other perinatal problems or conditions, some of which can also affect the immature hearing, e.g., neonatal meningitis, persistent pulmonary hypertension, treatments with ototoxic drugs, and hyperbilirubinaemia, resulting in sensorineural hearing impairment and hearing threshold elevation (Hall, 2007; Jiang, 2013; Kountakis et al., 2002; Mencher and Mencher, 1999; Marron et al., 1992; Meyer et al., 1999; Newton, 2001; Wilkinson and Jiang, 2006). In addition, middle ear disorders, typically middle ear effusion, may also partly account for the detected hearing abnormality (e.g., threshold elevation). Therefore, when interpreting the cause of hearing impairment in infants after perinatal asphyxia, one cannot simply attribute the hearing impairment exclusively to perinatal asphyxia.

The functional status of the immature auditory system can be assessed and monitored using non-invasive neurophysiological techniques, typically auditory evoked potentials, OAEs or DPOAEs (Hall 2007; Jiang, 2013; Kemp and Ryan, 1993; Norton, 2000a,b; Wilkinson and Jiang, 2006). These techniques can also be used to assess maturation of the auditory system and detect functional abnormalities or impairment of the system, typically after asphyxia. Among these neurophysiological techniques, BAER is the most commonly and widely used evoked potential to assess the developing auditory system and detect abnormality in clinical problems or conditions that may affect the brainstem auditory pathway. This article discusses the effects of perinatal asphyxia on peripheral hearing mainly in term infants. Particular attention is paid to the findings obtained using the BAER and DPOAEs. More recently, auditory neuropathy has attracted considerable interest. A brief

literature review was also made regarding whether perinatal asphyxia can cause auditory neuropathy in human infants. So far, there is a lack of reported full studies to demonstrate or confirm that perinatal asphyxia can cause auditory neuropathy.

PART I. BAER STUDIES

BAER Threshold and Perinatal Hypoxia or Hypoxia-Ischemia

Hearing threshold is inversely related to the magnitude of the endocochlear potential of the scala media in the inner ear, which partially determines auditory sensitivity (Gafni and Sohmer, 1976; Sewell, 1984). The endocochlear potential is generated by the sodium pump that has high energy requirements. Lack of sufficient oxygen supply to the stria vascularis suppresses the sodium-potassium pump and hence depresses the endocochlear potential (Gafni and Sohmer, 1976). As a result, the same sound intensity stimulus produces a smaller receptor potential and cochlear action potential, resulting in an elevation in hearing threshold. Hypoxia reduces auditory peripheral sensitivity and increases auditory threshold by depressing the endocochlear potential in the scala media of the inner ear (Sohmer et al., 1986). Early animal experiments showed that the auditory system could recover from hypoxia even during the critical period of endocochlear potential development (Cycowicz et al., 1988).

The BAER is a major clinically diagnostic tool for both hearing impairment in newborn infants with various perinatal conditions or problems, including asphyxia (Hall, 2007; Jiang, 2013). The threshold of BAER gives a good objective estimate of the amount of hearing loss, and has been widely used in audiometry in infants and children (Hecox and Cone, 1981; Jiang et al., 2001,2004a-c,2007,2011,2012a; Wang and Jiang, 2015; Yasuhara et al., 1986). It has been documented to be very sensitive to arterial blood oxygen content and hypoxia occurring during the perinatal period in both human studies and animal experiments (Sohmer et al., 1989,1994a,b; Sohmer and Freeman, 1991). Experiments in animal models showed that BAER threshold and auditory sensitivity are an inverse function of arterial blood oxygen levels (Sohmer et al., 1989). After perinatal asphyxia BAER threshold is often elevated, which can be interpreted as a reduction of auditory sensitivity due to a depression in the endocochlear potential. The elevation is a major pattern of abnormality in the BAER in both human neonates and animal models following hypoxia or hypoxia-ischemia (Sohmer and Freeman, 1991; Sohmer et al., 1989,1994a,b). In animals with experimental hypoxia, BAER threshold was found to be elevated during and immediately following hypoxia but returned to normal several hours later after breathing room air (Cycowicz et al., 1988). Similarly, in human neonates, BAER threshold was found to be elevated shortly after perinatal hypoxia-ischemia, and the elevation often recovers later (Jiang, 1995,1998; Jiang et al., 2004a).

Animal experiments revealed that BAER abnormalities following hypoxia are mainly due to ischemia even when the initial insult is hypoxic alone (Sohmer et al., 1986). Hypoxaemia has a direct effect on the cochlea and an indirect effect by way of cardiovascular collapse and cerebral ischemia (Sohmer et al., 1986). Persistent, particularly permanent, hearing impairment is primarily caused by prolonged periods of hypoxic-ischaemic insult secondary

to the hypoxia, as opposed to primary or direct hypoxic injury, and the complicated factors associated with hypoxia.

Change in BAER Threshold during the Neonatal Period

To explore the time course of change in hearing threshold during the neonatal period after asphyxia Jiang et al. (2004a) recorded serially the BAER from birth to the end of the first month in term infants who suffered perinatal asphyxia (Jiang et al., 2004a). As shown in Figs. 1 and 2, BAER threshold in infants after perinatal asphyxia was elevated significantly on day 1. The elevated threshold was decreased progressively on days 3 and 5, but was still significantly higher than in normal controls. The decrease, though slower, continued on days 10 and 15. The threshold approached to a normal level on day 30. These results suggest that hearing threshold in infants after perinatal asphyxia is significantly elevated on the first day after birth, and then decreased progressively. After day 5, the elevated threshold is continuously decreased, but more slowly with some variation. By the end of the first month, the threshold has nearly returned to normal. Clearly, the elevated threshold shortly after perinatal asphyxia is decreased progressively with the increase in postnatal age. Significant (i.e., moderate to severe) elevation of the hearing threshold occurs mainly during the first week, especially on day 1. Thereafter, significant elevation is very rare.

In some infants after perinatal asphyxia, BAER threshold elevation could occur and/or becomes more significant after the first 3-5 days after birth (Jiang et al., 2004a). This elevation is unlikely to be caused by perinatal hypoxic-ischaemic damage to the auditory system, but more likely to be due to middle ear disorders. This is because perinatal hypoxic-ischaemic damage to the auditory system is unlikely to start more than 3-5 days after birth. Thus, the slightly further elevation on day 7, shown in Figures 1 and 2, is at least partly explained by the occurrence of middle ear disorders. The extent of threshold elevation contributed to by hypoxia-ischemia should be less than the level of the elevation depicted in Figures 1 and 2. Although it is difficult to assess accurately the contribution of middle ear disorders to the elevation of BAER threshold, it is clear that peripheral hearing impairment due to hypoxic-ischaemic insult recovers progressively during the neonatal period.

The elevation in BAER threshold after perinatal asphyxia was generally more significant in infants who had severe hypoxic-ischaemic encephalopathy. However, the relationship between BAER threshold and the severity of encephalopathy varied with individuals (Jiang et al., 2004a). The infants who had severe encephalopathy were not necessarily associated with BAER threshold elevation. On the other hand, some infants who had mild encephalopathy were associated with significant threshold elevation. As shown in Figure 3, the group mean BAER threshold in infants with mild encephalopathy was slightly higher than in infants with moderate encephalopathy, although this difference did not reach statistical significance. BAER threshold correlated only weakly, though statistically significantly, with the severity of encephalopathy during the first 3 days, and did not thereafter.

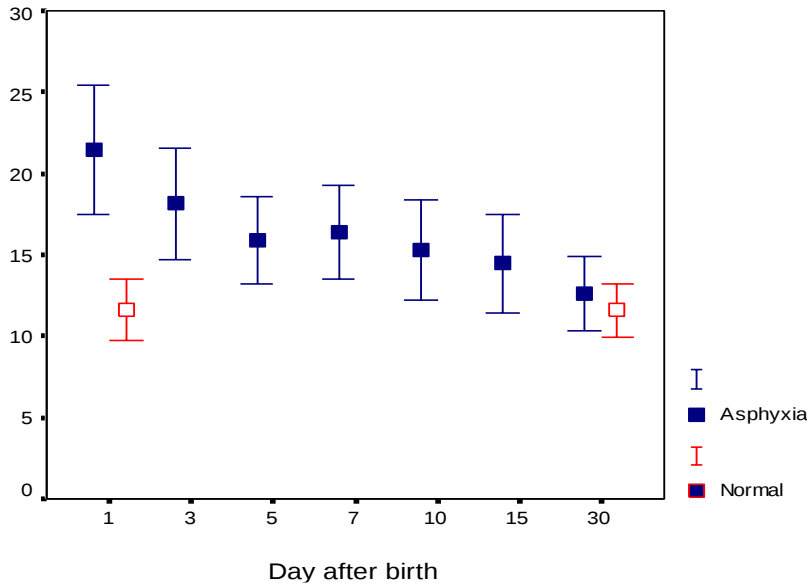


Figure 1. Group means and standard errors of BAER thresholds in infants after perinatal asphyxia on different days during the first month after birth. The BAER threshold in normal controls is almost the same on day 1-3 and day 30, whereas the mean threshold in the infants after asphyxia changes significantly with the increase in the day after birth. The mean threshold after asphyxia is elevated significantly on day 1. The elevated threshold is decreased progressively on day 3 and 5, but is still significantly higher than that in the controls. The threshold is elevated slightly further on day 7. Thereafter, the elevated threshold is continuously decreased more slowly on day 10 and day 15. By the end of the first month, the threshold is decreased to a level slightly higher than in the controls, and does not differ significantly between the asphyxiated and normal groups.

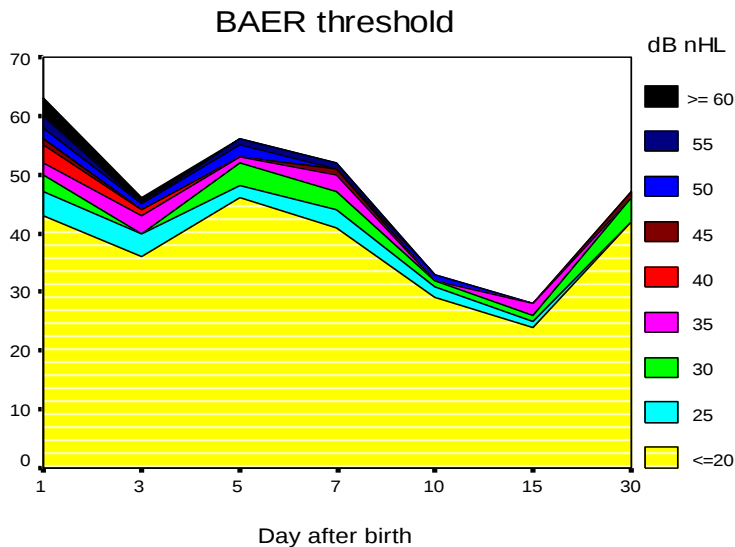


Figure 2. Distribution of BAER thresholds in infants after perinatal asphyxia on different days during the first month after birth. Throughout the first month, most of the infants after asphyxia have a BAER threshold within normal range (≤ 20 dB nHL). On day 1, nearly one-third (31.7%) of the infants show threshold elevation (i.e., > 20 dB nHL). Thereafter, the rate of the elevation is decreased progressively. On day 30, only 10.6% of the infants show threshold elevation.

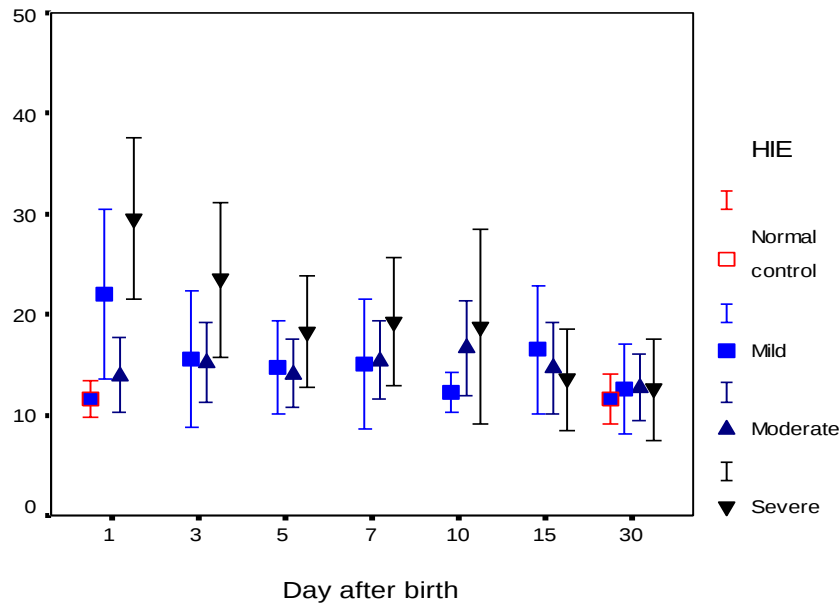


Figure 3. Means and standard errors of BAER thresholds in infants with different (mild, moderate and severe) degrees of hypoxic-ischaemic encephalopathy after perinatal asphyxia on different days during the first month after birth. Within the first 10 days, BAER elevation is always most significant in infants with severe encephalopathy. There is a significant difference in BAER threshold among different degrees of encephalopathy on day 1, but not on any other days. The threshold in infants with severe encephalopathy is significant higher than in infants with mild and moderate encephalopathy on day 1 and on day 3. No significant difference is found on any other days.

These findings suggest that hearing threshold after perinatal asphyxia does not correlates closely with the severity of brain damage. There are at least two possible explanations of this weak correlation. One is that there are individual differences in the vulnerability of peripheral auditory system and central system to hypoxic-ischaemic insult. The other is that threshold elevation which is related to other confounding factors, particularly middle ear disorders, can occur in infants with or without hypoxic-ischaemic brain damage. The threshold elevation starting after days 3-5 is more likely to be due to middle ear disorders, although the elevation during the first 3 days is most likely to be caused by or related to hypoxic-ischaemic damage to the peripheral auditory system.

Prevalence of Hearing Impairment during the Neonatal Period

The prevalence of hearing impairment in infants after perinatal asphyxia has been reported to be varied widely (e.g., Abramovich et al., 1979; Anagnostakis et al., 1982; Flint, 1983; Hecox and Cone, 1981; Jiang et al., 2004a; Mencher, et al., 1981; Yasuhara et al., 1986). In Flint's report (1983), hypoxia induced hearing impairment accounted for 36% of the perinatal incidence. It seems that perinatal hypoxia is the most important cause of perinatally acquired hearing impairment. Mencher, et al. (1981) and Robertson and Whyte (1983) found that nearly 30% of the congenital hearing impairment was related to hypoxia. Hecox and Cone (1981) reported that peripheral hearing impairment occurred in 20% of infants within 3 months

after the onset of asphyxia. The study by Yasuhara et al. (1986) found that as high as 67% of the infants with severe asphyxia demonstrated threshold elevation. In contrast, some others described an incidence of hearing impairment as low as 9% (Abramovich et al., 1979; Anagnostakis et al., 1982). The considerable variation in the reported prevalence of hearing impairment (between 9-67%) are largely related to the differences in the population studied, the severity of asphyxia, and the age or the time after birth at which the subjects were examined among various studies. It should be noted that hearing threshold elevation and impairment in infants after perinatal asphyxia can be related to or due to other associated perinatal complications or risk factors, not exclusively asphyxia. Most previous investigators did not describe whether they had strictly excluded other perinatal complications that may cause hearing impairment and confound their results. Therefore, there might be certain bias in the reported prevalence of hearing impairment due to perinatal asphyxia.

After perinatal asphyxia, with the improvement of clinical condition the elevated BAER threshold usually returns to normal or near normal. Figure 2 shows the distribution of term infants with different BAER thresholds after perinatal asphyxia on day 1 through to day 30 after birth (Jiang et al., 2004a). Elevation of BAER threshold occurred in 31.7% of the infants on day 1, and 34.5% during the first 3 days, suggesting that hearing threshold is elevated in about one-third of term infants after perinatal asphyxia (Jiang et al., 2004a). Thereafter, the rate of elevation was decreased progressively. By the end of the first month, the elevated threshold in most infants has returned to a near normal level, with only 10.6% of the infants showing threshold elevation. Moderate to severe elevation occurred mainly during the first week and severe elevation occurred predominately on day 1. Taken together, peripheral hearing impairment, which is related to hypoxic-ischaemic insult, occurs in about one-third of the infants after perinatal asphyxia during the perinatal period. The impairment persists in about one in ten of the infants by the end of the first month after birth.

Postnatal Change in BAER Threshold

After the first month, the elevation of hearing threshold due to perinatal asphyxia recovers further in most infants. Jiang (1998) followed BAER during the first year of life in 44 infants who suffered perinatal asphyxia. The postnatal change in BAER threshold was generally similar to that in normal controls, i.e., the threshold was decreased with an increase in age, with a rapid change occurring at the first three months. However, the threshold, particularly in severe asphyxiated infants, was higher compared to normal controls, mainly at the first three months. In those asphyxiated infants who had a threshold elevation (greater than 20 dB HL), the latency-intensity functions for wave V were different from the age-matched normal controls at low stimulus intensities and the difference was much smaller at high intensities, suggesting sensorineural hearing impairment. At 3 months of age, BAER threshold elevation was seen in 4.3% of the infants after mild asphyxia and 9.5% of the infants after severe asphyxia. Thereafter, the elevated BAER threshold in these infants did not show any further significant improvement. These observations indicate that after perinatal asphyxia the elevated hearing threshold occurring shortly after birth continues to improve up to about 3 months post term. Thereafter, the threshold elevation, which occurs only in a few cases, often does not show any further significant improvement, suggesting persistent or permanent hearing impairment.

Persistent or Permanent Hearing Impairment

Previous studies showed that persistent or permanent hearing impairment occurs in only a small proportion of the infants or children after perinatal asphyxia (Jiang, 1995,1998; Jiang et al., 2004a; Zheng and Jiang, 1992). In an effort to explore the long-term effect of asphyxia on the development of infant's hearing, Jiang (1995) examined BAER in children who survived perinatal asphyxia. Most of these children had a BAER threshold less than 20 dB nHL. In 48 children without developmental delay or cerebral palsy, only 3 (6.8%) exhibited a slightly elevated response threshold (>20 dB nHL). In 41 children with developmental delay or cerebral palsy, BAER threshold was generally higher than those without developmental delay or cerebral palsy. 7 (17.1%) children had a BAER threshold greater than 20 dB nHL, which was higher than in those children without developmental delay and cerebral palsy (6.5%). It appears that there was some coincidence in the occurrence of peripheral hearing impairment and residual neurodevelopmental deficits, although this correlation was not statistically significant (Jiang, 1995).

The latencies of BAER waves are generally normal in the children with a normal threshold after perinatal asphyxia, but prolonged in those with threshold elevation. The latency and latency-intensity function for wave V in the children with threshold elevation often show a large difference from the age-matched normal controls at low click intensities, whereas the difference is much smaller at high intensities (Jiang, 1995). Such a characteristic change in the latency-intensity function is indicative of sensorineural hearing impairment.

The prevalence of persistent or permanent hearing impairment is higher in the children after severe perinatal asphyxia than in those after mild asphyxia (Jiang, 1995). Nevertheless, this prevalence is not closely related to the degree of perinatal asphyxia. This is consistent with clinical observations of the relationship between the occurrence of neurodevelopmental deficits and the severity of perinatal asphyxia. Neurodevelopmental deficits occur not only after severe perinatal asphyxia but also occur after mild asphyxia. Some children with mild perinatal asphyxia exhibit residual neurodevelopmental deficits, while many children with severe asphyxia may develop without any apparent residual deficits. This relatively poor relationship is at least partly interpreted by the susceptibility to hypoxia that varies among individuals. In addition, the occurrence of hypoxic injury to the auditory system depends on the duration as well as the degree of asphyxia.

To detect any differences in the effect of perinatal and postnatal asphyxia on the developing auditory system, Jiang (1995) examined BAER in children who survived severe, prolonged postnatal asphyxia due to serious pneumonia associated with severe hypoxia and respiratory failure, aspiration of foreign bodies with severe hypoxia, or drowning. These children exhibited residual neurodevelopmental deficits. In contrast to those who survived severe perinatal asphyxia, the children survived postnatal asphyxia did not show any evidence of permanent peripheral hearing impairment. It seems that a critical period of particularly sensitive to the effect of hypoxia may exist during the development of human peripheral auditory system. This period may range from some time prenatally to some time shortly after birth, probably the third postnatal month (Jiang and Tierney, 1995). After the critical period, hypoxia is unlikely to lead to permanent peripheral hearing impairment.

The exact sites of lesions in the auditory pathway in children with hearing impairment after perinatal asphyxia remain to be determined. Orita et al. (2002) conducted a histopathologic examination on the temporal bones in a patient with severe bilateral

sensorineural hearing impairment after perinatal and postnatal hypoxia and asphyxia. In the left temporal bone, there were severe atrophy of the organ of Corti throughout the entire cochlea, decrease in the number of the spiral ganglion cells especially in the basal turn, and mild atrophy of saccular macula. In the right temporal bone, similar but milder abnormalities were observed in the inner ear. No other distinct pathologic finding was observed in either ear. These findings suggest that the presence of severe hypoxia-ischemia causes cochleosaccular atrophy in the inner ear. Such pathology could manifest elevation in BAER threshold and prolongation in BAER wave latencies, and abnormality in OAEs or DPOAEs.

PART II. DOAEs STUDIES

DPOAE Changes and Cochlear Impairment

Understanding of what frequencies on the audiogram of the cochlea are affected by asphyxia is important for intervention of hearing impairment after perinatal asphyxia. The BAER, which is elicited commonly by click stimuli, lacks frequency-specificity, and cannot identify which frequencies of the cochlear audiogram are affected in the cases with hearing impairment. In contrast, DPOAEs can objectively assess frequency-specific hearing, and have been widely used to examine cochlear function (American Academy of Pediatrics, 1999; Joint Committee on Infant Hearing, 1995,2000; Salata et al., 1998). The DP audiogram has proven useful in estimating audiometric configuration (Gaskill and Brown, 1993; Kimberley et al., 1994; Lonsbury-Martin and Martin, 1990). The frequency pattern of DPOAE amplitude reduction or absence often follows the configuration of hearing impairment in the audiogram. DPOAEs, which can be obtained quickly, have now become a widely used objective audiometric tool to assess infant's cochlear function and identify hearing impairment (Berg et al., 2005; Cone-Wesson et al., 2000; Gorga et al., 2000; Jiang et al., 2012b; Joint Committee on Infant Hearing, 1995,2000; Kemp and Ryan, 1993; Mencher and Mencher, 1999; Norton et al., 2000a,b; Vatovec et al., 2001). The emissions are absent when hearing impairment due to cochlear pathology is 45 to 50 dB or greater (Sininger and Abdala, 1998). Early experiments showed that hypoxia for a few minutes can severely inhibit OAE (Frolenkov et al., 1998; Kemp and Brown, 1984; Whitehead et al., 1992). Severe or lethal hypoxia can result in the DPOAEs disappearing at low-level stimulation (45–60 dB sound pressure level - SPL), as a result of the damage of cochlea (Rebillard et al., 1993).

Severe hypoxemia has a direct effect on the cochlea and an indirect effect by way of cardiovascular collapse and cerebral ischemia (Sohmer et al., 1986). The effects may lead to sensory or sensorineural hearing impairment, although the impairment is mostly temporary (Jiang, 1998; Jiang et al., 2004a). Previous BAER studies in experimental animals suggests that peripheral hearing impairment after hypoxia is reversible and the recovery occurs soon after the termination of hypoxia (Sohmer et al., 1994a; Sohmer H, Freeman, 1991). Similar finding was observed in the human fetus (Sohmer et al., 1994b). However, permanent sensorineural hearing impairment does happen in some infants after perinatal asphyxia (Jiang, 1995; Sano et al., 2005). For these infants, selection and implementation of a proper plan to intervene in hearing impairment, e.g., fitting a hearing aid or performing a cochlear implant, requires accurate information about the hearing impairment at all frequencies important for

speech and language development. Thus, it is crucial to obtain detailed information about cochlear function in the infant or child who has hearing impairment.

DPOAE Changes after Perinatal Asphyxia

To elucidate what frequencies in the cochlear audiogram are susceptible to perinatal asphyxia we studied DPOAEs across the frequencies between 0.50 and 10 kHz during the first postnatal year in term infants who suffered perinatal asphyxia (Jiang et al., 2005, 2012b; Zang et al., 2008). DPOAEs were obtained serially at 3-5 days after birth, and 1, 6 and 12 months of age to examine functional status of the cochlea and depict a picture of age-related postnatal changes in DPOAE and, in turn, cochlear function after perinatal asphyxia.

DPOAEs at 3-5 days after birth. DPOAE pass rates across the frequency range between 1 and 10 kHz, particularly at 1-5 kHz in the infants after perinatal asphyxia were all significantly lower than in age-matched normal term controls. The overall DPOAE pass rate (83.7%) was also significantly lower than in normal controls (95.7%). In normal infants DPOAE pass rate was decreased with the decrease in the frequency of the f_2 primary tone (Zang and Jiang, 2007). In the infants after perinatal asphyxia DPOAE pass rates at various frequencies showed a similar trend, although the decrease was more significantly. The pass rates, particular at 1-5 kHz, were much lower than in normal infants. The overall DPOAE pass rate was also lower. Obviously, perinatal asphyxia suppresses neonatal DPOAEs at the frequencies across 1-10 kHz, mainly 1-5 kHz.

DPOAEs at 1 month. The infants after perinatal asphyxia showed a further decrease in DPOAE pass rates at all frequencies (Jiang et al., 2005). This was more significant at 1 and 2 kHz than at other frequencies. The overall DPOAE pass rate (83.8%) was the same as that on days 3-5 (83.7%). It seems that the frequency-specific hearing impairment detected on days 3-5 after birth remains or even slightly worsens at the later neonatal period. 8.8% of the tested ears with a type A tympanogram (i.e., without middle ear disorders) failed the DPOAE test, suggesting that nearly 10% of the infants after perinatal asphyxia have hearing impairment that persists for at least 1 month. It seems that the cochlear impairment detected on days 3-5 after birth is unlikely to improve or even slightly worsens in the later neonatal period. This is in agreement with our finding of 10.6% of the asphyxiated infants showing BAER threshold elevation on day 30 after birth, i.e., one in ten having persistent hearing impairment (Jiang et al., 2004a).

DPOAEs at 6 months. DPOAE pass rates, mainly at the frequencies 1-4 kHz, in the infants after perinatal asphyxia were lower than those in age-matched normal infants (Zang et al., 2008). The overall DPOAE pass rate (81.8%) remained lower, compared with that (98.5%) in normal controls. Apparently, there is still a certain degree of impairment in cochlear function at 6 months after birth in the infants who suffer perinatal asphyxia.

The general pattern of DPOAE pass rates at various frequencies at 6 months was similar to that obtained at 1 month of age (Jiang et al., 2005). The same was true of overall DPOAE pass rate. However, compared to those at 1 month, DPOAE pass rates at 6 months were increased at almost all frequencies. The increase was statistically significant at 3, and 5-8 kHz. Thus, DPOAE pass rates in the infants after perinatal asphyxia has demonstrated some improvement. With time passing, the cochlear impairment due to perinatal asphyxia tends to

recover, but there still is a certain degree of impairment, mainly at 1-4 kHz, at 6 months of age.

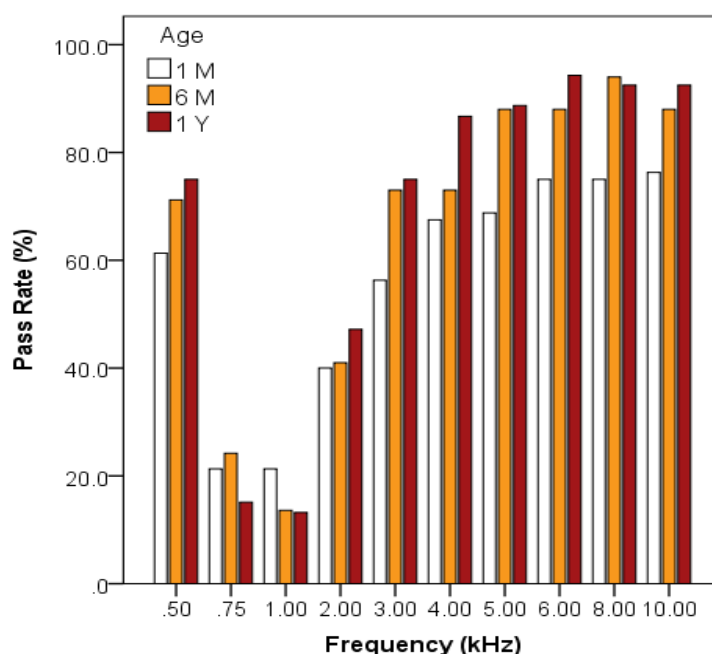


Figure 4. DPOAE pass rate (%) at various frequencies of the f_2 primary tone in infants after perinatal asphyxia during the first year of life. The date of DPOAEs on days 3-5 after birth are not included because no tympanometry was performed at that time and, thus, a possible certain effect of middle ear disorders in some infants on DPOAEs cannot be excluded. As the age increases from 1 month onwards, the pass rates at most frequencies tend to be increased, suggesting some improvement in cochlear impairment with time passing.

DPOAEs at 1 year. Compared to age-matched normal infants, the infants after perinatal asphyxia showed similar pattern of the pass rates at various frequencies of the f_2 primary tone, but the pass rates at most individual frequencies remained lower (Jiang et al., 2012b). DPOAE pass rates in the infants after perinatal asphyxia were decreased at all frequencies of the f_2 primary tone between 0.75 and 10 kHz, particularly at 1 and 2 kHz. The pass rates at all 1-10 kHz, except for 6 kHz, of the f_2 primary tone were significantly lower than those in the controls (Figure 4). The greatest difference occurred at the frequencies 1 and 2 kHz. The overall DPOAE pass rate in the infants after perinatal asphyxia (84.9%) was significantly lower than the rate in the controls (100.0%). These results suggest that after perinatal asphyxia cochlear function, particularly at 1 and 2 kHz, remains relatively poor at 1 year of age.

Compared to those at 6 months after perinatal asphyxia, DPOAE pass rates at 1 year were increased at most frequencies, with a statistically significant difference at 0.5 kHz. The overall DPOAE pass rate at 1 year (84.9%) was slightly greater than at 6 months (81.8%). Thus, during the second half of the first year of life the impaired cochlear function in infants born with perinatal asphyxia is slightly improved. As a whole, at 1 year DPOAE pass rates at most frequencies tended to be increased when compared with those obtained at earlier ages. It appears that following the hypoxic-ischemic insult during the perinatal period, the impairment

in cochlear function improves slightly with time passing during the first postnatal year of life. By the end of first year, there is still a certain degree of cochlear impairment.

Persistent decrease in cochlear function at 1 and 2 kHz. The above DPOAE results in term infants after perinatal asphyxia during the first year of life depict a picture of postnatal changes in DPOAEs and, in turn, cochlear function after perinatal asphyxia. We pooled together the DPOAE data, obtained at different ages during the first 1 year, and plotted the data in Figure 4 showing postnatal changes in DPOAEs after perinatal asphyxia (Jiang et al., 2005; Zang et al., 2008). There is a tendency of increase in DPOAE pass rates at almost all frequencies of the f_2 primary tone from 1 month to 1 year of age although the pass rate at 1 kHz was decreased slightly. These longitudinal DPOAEs studies demonstrated that perinatal hypoxia-ischemia adversely affects functional status of the cochlea, specifically the outer hair cells. Within the first few days after birth, cochlear function is mainly affected or impaired at 1-5 kHz, particularly 1 and 2 kHz, suggesting that hypoxic-ischemic insult occurring during the perinatal period adversely affects newborn cochlear function. During the postnatal development, there is only a slight improvement in the cochlear impairment. By the end of the first year, cochlear function, mainly at 1 and 2 kHz, remains relatively poor. It appears that cochlear impairment attributable to perinatal asphyxia is unlikely to completely recover in some infants. These findings contribute to our understanding of the effect of perinatal asphyxia on cochlear function. The finding of persistent impairment at 1 and 2 kHz during the first year of life provides valuable information for early interventions of hearing impairment in infants after perinatal asphyxia, particularly for hearing aid fitting or cochlear implant that requires accurate information about the hearing impairment at all frequencies important for speech and language development.

PART III. AUDITORY NEUROPATHY

The most common type of permanent hearing impairment is sensorineural hearing impairment. Auditory neuropathy, also known as Auditory Dysynchrony or Auditory Neuropathy Spectrum Disorder, is a less common type of hearing impairment. It was first identified in the 1980s when OAEs became available to measure cochlea function. It is a hearing disorder where outer hair cell function within the cochlea is normal, but inner hair cell and/or the auditory nerve function is disrupted. The exact site of lesion for auditory neuropathy remains to be determined. The possibilities include cochlear inner hair cells, cochlear spiral ganglia, the synapse between the inner hair cells and the auditory nerve and the auditory nerve (Starr et al., 1996).

Auditory neuropathy is a heterogeneous disorder which can have either congenital or acquired causes. The aetiology of auditory neuropathy is vast, which may include prematurity, hyperbilirubinaemia, anoxia, hypoxia, congenital brain anomalies, ototoxic drug exposure, and genetic factors. It is estimated that the largest proportion (approximately 40%) of auditory neuropathy have an underlying genetic basis, which can be inherited in both syndromic and non syndromic conditions (Manchaiah et al., 2011). Different gene mutations may trigger different pathological changes in patients with auditory neuropathy.

In experimental animal studies, there is evidence suggesting that perinatal anoxia or hypoxia can result in auditory neuropathy. Harrison (1998) described an animal model of

auditory neuropathy in which subjects have extensive, scattered inner hair cell loss but with a relatively intact outer hair cell population, produced in the chinchilla by treatment with the anticancer agent carboplatin. They found that in these chinchilla, OAEs and cochlear microphonics remained normal while BAER thresholds were significantly elevated. However, the response thresholds in the central auditory neurons (in the inferior colliculus) were considerably lower (by up to 50 dB) than BAER thresholds. The authors suggested that scattered inner hair cell lesions can also result from long-term cochlear hypoxia, which is likely candidate for the etiology of many types of auditory neuropathy in human subjects.

Later, Sawada et al. (2001) examined the effects of long-term mild hypoxia and of glutamate poisoning on the functional properties of the cochlea. They used OAEs and cochlear microphonics to monitor outer hair cell activity and used cochlear action potentials or BAER to measure inner hair cell/cochlear afferent function. In contrast to the effects of acute anoxia, in which all aspects of cochlear function were simultaneously lost, mild long-term hypoxia resulted in a clear differential effect on outer versus inner hair cell systems. During a 2-hour period of mild hypoxia, BAER amplitude and threshold deteriorates significantly, whereas outer hair cell function, as reflected by otoacoustic emissions, showed little or no change. A similar dissociation between inner and outer hair cell function was observed during instillation of glutamate, where the cochlear microphonic and the otoacoustic emissions were unchanged, whereas cochlear action potential amplitudes were reduced. Thus, there was a difference in vulnerability of inner and outer hair cell systems. The inner hair cell/cochlear afferent system is vulnerable to long-term, mild hypoxia; this may be an etiologic factor in hearing impairment of cochlear origin, particularly in high-risk birth infants with auditory neuropathy.

Whether perinatal asphyxia can cause auditory neuropathy in human infants remains to be determined. Although perinatal asphyxia has been suggested to be a possible risk factor of auditory neuropathy in infants (Xu et al., 2011), so far there is a lack of reported full studies in human infants to demonstrate or confirm that perinatal asphyxia can result in auditory neuropathy. This is certainly an interest area to be explored.

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Chapter 9

“I WILL MAKE A DIFFERENCE”: USING THE 5AS MODEL TO IMPROVE ISSUES FOR ADULTS WITH LEARNING DISABILITIES AND HEARING LOSS

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ABSTRACT

This chapter details a piece of original qualitative research, designed to improve audiological issues for adults with learning disabilities and hearing loss who are supported by paid caregivers. The research study comprised of four action research cycles. The first cycle involved visiting and interviewing paid caregivers in their workplace to explore their baseline knowledge and experience of hearing loss and hearing aids. Findings indicated that the majority of participants underestimated the prevalence of hearing loss and had inaccurate knowledge regarding assessment and hearing aids. Symbolic interactionism was used as a theoretical tool to account for their perspectives.

The second cycle involved designing and piloting a training package for a wider group of caregivers. The content and delivery of the training was informed by suggestions from participants of cycle one and other key stakeholders. Situated learning and experiential learning theory were the theoretical basis for the training design. 44 individuals were trained across 6 homes and constant refinement of the training occurred throughout the pilot phase. Early indications were positive; participants' knowledge and confidence increased post training and pledges were made to continue the change process.

The third cycle was concerned with evaluation of the effectiveness of the training. Follow up visits were made to each home and a reassessment of knowledge and confidence suggested the improvements had largely persisted. Within six months, 96% of all pledges made had been achieved and the estimated prevalence of hearing loss in those supported by staff increased from 23 to 54%, with several new confirmed diagnoses of hearing loss. Focus group discussions were held with staff to explore their experiences

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post training. Many described “new chapters” in their working lives, suggesting they had completed their own cycle of experiential learning. These discussions also revealed barriers to Audiology within primary care which necessitated investigation in a further cycle.

The fourth cycle involved visiting and interviewing primary care practitioners in their workplace in order to explore their experiences, in a similar manner to cycle one. Findings from this group suggested a significant underestimation of hearing loss in people with learning disabilities and negative attitudes around the worth and benefit of referral.

This study has shown that training in audiological issues can evoke a change in working practice, which had not been demonstrated in the literature prior. Contact between caregivers and Audiology was also important and the need to develop the role of Audiology within the community, transpired as one of the key findings of this research. Theoretical development of the findings has led to creation of a conceptual model (the 5As model), which acknowledges the need for multidisciplinary engagement in assessment and management of hearing loss in people with learning disabilities. Though the model was created for hearing issues, it has broader application and relevance across other health disciplines.

Keywords: hearing, caregiver, audiology, training, primary care, 5As model

1. INTRODUCTION

Hearing loss is the partial or total inability to perceive (hear) sounds. The spectrum of hearing loss is vast, ranging from individuals with no hearing, to those with partial hearing loss affecting only certain pitches of sound. The consequences for any individual with hearing loss can include increased mortality, poorer health and poorer quality of life (McCormack & Fortnum, 2013). Hearing aids are the most common “treatment” for hearing loss and due to improved technology, cosmetic appearance and increased awareness, more people are seeking hearing aids than ever before. However, this is not the case for people with learning disabilities, despite high levels of need (McShea, 2013). Audiological research into the assessment and support of people with learning disabilities is lacking (McCracken et al., 2011).

1.1. Coexistence

People with learning disabilities are much more likely to have a hearing problem than the general population. Syndromes involving both hearing loss and learning disability are relatively common (e.g., Down’s syndrome). Not only is permanent hearing loss more likely in people with learning disabilities (Hild et al., 2008), but this group are also more prone to ear infections, structural ear abnormalities and wax occlusion (Hardy et al., 2011; Fransman, 2006). The exact prevalence of hearing loss in people with learning disabilities is unknown. The most commonly used estimate is 40% (Emerson et al. 2012), though this is likely to be an underestimate, as many of the studies that have published estimates of prevalence have arrived at these figures by review of medical records or interview alone (Bent et al., 2015). High risk groups (e.g., individuals with Down's syndrome) are thought to experience a

prevalence of hearing loss between 50-100% (Miller & Kiani, 2008). Despite this need, the majority of this population have never had their hearing tested (Hardy et al., 2011).

1.2. Hearing Loss with Learning Disabilities; Double Jeopardy

For any adult with a hearing loss, there are individual and social consequences (Hindhede, 2011). If that hearing loss is unknown or undiagnosed, it affects the potential of that individual and underestimates their abilities (Van Schrojenstein Lantman-de Valk, 2005). There are many overlapping features of hearing loss and learning disability, for example reduced comprehension and communication, frustration, and reduced social engagement (Pryce & Gooberman-Hill, 2012). The relationship between learning disability and hearing loss is thought to be multiplicative rather than additive (Carvill, 2001). The combined effect of having both "conditions" is greater than their sum. This means, it is even more imperative that hearing loss is not underestimated by those involved with people with learning disabilities. In many cases, the degree of a person's learning disability may be less severe than first thought, following diagnosis and treatment of hearing loss (Sigafos, 2000). Providing habilitation for hearing loss can improve quality of life considerably and unexpectedly (McShea et al., 2014).

1.3. Conceptualising the Issue; the 3As

With hearing loss so common in people with learning disabilities, and its effect so profound, it is imperative that detection improves. I created a model, termed "the 3As" to conceptualise this complex situation. The 3As are Access, Assessment and Aftercare and are relevant to any health discipline:

- **Access** - Individuals with learning disabilities and their advocates must have an awareness of the prevalence of hearing loss, must be able to identify hearing loss and be able to access appropriate referral to specialist services, via a General Practitioner (GP).
- **Assessment** - Once known to specialist services (e.g., Audiology), attendance should be facilitated, and accurate, successful diagnostic testing should be achievable.
- **Aftercare** - Following diagnosis of hearing loss, management and rehabilitation should be appropriate and adhered to. This may include use of hearing aids, assistive listening devices and adherence to any follow up appointments.

1.3.1. Understanding Access

Prior to accessing services, there needs to be identification of a problem (for example, difficulty hearing). In the UK, primary care requires an element of self-referral and motivation (Newsam et al., 2010). This in itself is the first barrier to access (Felce et al., 2008). People with learning disabilities may not have the communication skills to seek referral for their own health needs, if indeed there are even aware of a need themselves. Therefore, the onus is on another relevant individual close to that person usually the

“caregiver”, to recognise the problem and access appropriate services on their behalf. Clearly, this relies on the individual and their caregiver communicating effectively and the caregiver having the skills to detect hearing loss. However, caregivers often misjudge the communication abilities of people with learning disabilities (Banat et al., 2002; Kevan, 2003).

Although the clues of hearing loss are usually present, they are often attributed to the known learning disability (“diagnostic overshadowing”, Carvill 2001). There is plentiful evidence in the literature (e.g., Kerr et al., 2003), to suggest that most caregivers cannot recognise hearing loss in those they support. The more severe a learning disability, the more likely a hearing loss is to be overlooked (Carvill, 2001). For people with learning disabilities who do access services either directly or by proxy, some responsibility also lies with primary care regarding their attitudes and beliefs surrounding the worth of referrals to specialist services (Lindsey, 2002). As GPs are “gatekeepers” to services, their input is vital, not only for access, but also assessment.

1.3.2. Understanding Assessment

The initial assessment begins in the GP consultation. It is up to the GP to decide whether referral to specialist services is necessary. Cook & Lennox (2000) suggest 92% of GPs find it difficult to obtain a clear medical history from the individual or their caregiver and that care suffers significantly as a result. Not only do these authors advocate further training of GPs, but also place some responsibility on the attending caregiver. Lennox et al. (1997) stress the importance of having familiar and knowledgeable caregivers attend assessments.

There is a misconception people with learning disabilities cannot have their hearing tested, perhaps because historically, assessment has been suboptimal (McMillan et al., 2000). However there are a range of techniques now available in contemporary Audiology (McShea, 2013) which means it is incorrect to label someone as “untestable”. Audiology assessment is the most accurate way of detecting the presence of hearing loss. Lavis et al. (1997), found that prevalence of hearing loss was between 13-73% when formal assessment methods were employed, compared to 7-20% when relying on staff opinion or questionnaire.

1.3.3. Understanding Aftercare

Even if the barriers of accessing a service and completing an assessment are overcome, the worth of this is called into question if aftercare is not sufficient. Even in the general population, first time hearing aid users report feeling overwhelmed and leave the appointment with both informational and support needs (Kelly et al., 2013). If these needs are not fulfilled by aftercare, it is likely rejection of the device will occur. For many, this outcome could be avoided with better training (Gianopoulos et al., 2002). If this is the case for individuals who have the self-motivation to attend; it is perhaps even more likely to occur for individuals who rely on others to meet their needs. There are misguided assumptions that people with learning disabilities will not tolerate hearing aids or benefit from them (Meuwese-Jongejeugd et al., 2007). Evidence is available to show hearing aid benefit (e.g., Coppens-Hofman et al., 2013), but this evidence has not been translated from professional to individual (or caregiver). Without this, how can we expect people to comply?

Though Audiology professionals have a duty to cascade information to patients and their caregivers, they are relatively powerless outside of the clinic as to what happens. In the home environment, this responsibility shifts to the individual or their caregiver. However, paid caregivers have difficulties understanding the use and maintenance of hearing aids (Miller &

Kiani, 2008). Even those who experience hearing aids as part of their work have poor practical skills (Rocks & Ferguson, 2014). A survey by Pryce & Gooberman-Hill (2013) revealed that 44% of staff working with elderly hearing aid users, did not know how to fix broken devices. Many people with learning disabilities also rely on caregivers to be responsible for their hearing aid care. Training is recommended around the purpose of hearing aids, their function and correct maintenance (Meuwese-Jongejeugd et al., 2007). Because caregivers are integral to successful aftercare, this barrier must be overcome and meaningful engagement with caregivers must be achieved.

This research had two broad aims:

1. To improve the awareness and practice of paid caregivers with respect to hearing loss and Audiology using training.
2. To evaluate the effectiveness of this training and determine the key factors in this.

2. METHODOLOGY

Action research was my chosen methodology for this study, as it has real emphasis on change. It can be viewed as a holistic methodology; not only regarding inclusion of a wider community, but also in its approach to problem identification, investigation and change. I am unaware of any other research within Audiology that has used action research methodology. An increase in qualitative research is occurring in Audiology (Knudsen et al., 2012), and Ng (2013) advocated inverting the hierarchy of evidence, to give more weighting to alternative methodologies which could explore and understand the experiences of individuals. Moodie et al. (2011), feel that collaboration with service users represents a more modern way of conducting research in Audiology.

Action research stems from a critical theory paradigm; which is not only concerned with examining practice but also wider influencing factors (Fulton et al., 2013). Critical theory does share some commonalities with interpretivism, such as qualitative information gathering and appreciation of values and experience. Though interpretivists use qualitative information, the researcher remains objective and impartial (Koshy et al., 2011). In critical theory, the researcher takes a conscious and active role, and believes value can be obtained from this (McNiff & Whitehead, 2011). I felt this approach was preferable as it helped to demonstrate the collaborative nature of hearing loss between caregivers and Audiology and aimed to reduce any power differential that may have been felt. Action research embraces context (Baum et al., 2006), tacit knowledge and experience (Stringer, 1999). By including such opinions and experiences, people have a genuine voice and influence (McIntosh, 2010), meaning the elite position of the researcher is reduced. By involving caregivers directly in the research, a sense of ownership may mean initiatives are more likely to be adopted.

Action research has often been credited with bridging the gap between theory and practice (Holter & Schwartz-Barcott, 1993). One of the strengths of action research clearly lies in its flexibility and responsiveness. All action research has certain elements of commonality; a holistic and iterative nature, with modifications and evaluations influencing subsequent cycles. The cyclical and reflective nature of action research is important. It ensures that action is timely and relevant and provides a robust framework for understanding

complex situations (Reason & Bradbury, 2008). This research was completed using four cycles, with ethical approval for the whole study granted by the University of Sunderland:

- Cycle 1 – Defining the problem
- Cycle 2 – Designing and piloting a solution
- Cycle 3 – Evaluating the solution
- Cycle 4 – Investigating an unexpected issue

3. CYCLE 1 – DEFINING THE PROBLEM (SEE MCSHEA ET AL., 2015)

In order to work collaboratively with caregivers, this first cycle was necessary to gain an understanding of their baseline knowledge. I feel caregivers are central to access and aftercare in the 3As model. Did they agree? What did they know about hearing problems and hearing aids? An appreciation of their knowledge and beliefs meant it would be possible to work together more effectively.

Qualitative methods are valuable in providing rich and deep information about the experience of individuals (Bryman, 2016). Semi-structured interviews were the method chosen for this cycle, preferable to group interviews when discussing personal or sensitive topics (Patton, 2015). They also allow specific issues to be addressed, and are recommended for use in action-orientated research (Bryman, 2016). I felt that I approached Cycle 1 with clear subject areas to be addressed (such as knowledge of Audiology, attitudes towards hearing aids, etc.) and could therefore use semi-structured interviews in a focussed manner.

3.1. Recruitment of Caregivers

Caregivers were recruited following an online search for registered care facilities (n = 40) and a recruitment mailing to each one. Though collaboration was a later goal, care managers may have felt the initial postal contact was random and unexpected. However, for ethical purposes, it was not appropriate to contact facilities I was aware of or had come into contact with as a result of my clinical work. Once contact had been made, it was important to ensure participants felt involved and empowered. I chose the wording of documents carefully, focussing on improvements rather than problems, and emphasised the need for collaboration. A return of 18% was achieved and 6 facilities were visited.

With each facility I attended, I was usually required to meet and speak to the manager first. This was a brief conversation, confirming the purpose of my visit and my requirements. The manager then introduced me to other staff present and showed me to a room appropriate for the interviews. In most cases, this was the dining room. I explained the purpose of the interview to each participant and asked them to sign a consent form. This included notice of the use of a recording device and possible verbatim quotations. The device was placed carefully, to minimise its intrusive nature. Information sheets were available, along with the opportunity to ask questions and withdraw at any time. Questions covered several areas including:

- Basic demographic information
- A contemporary caregiver’s role
- Questions about hearing loss
- Experiences of training to engage caregivers in the next research cycle

Although the main subject areas were covered with all interviewees, the exact wording and question order were flexible. Twenty members of staff were interviewed across the six facilities. Almost every interviewee had a National Vocational Qualification (NVQ) in Health and Social Care, and all were engaged in mandatory training. Analysis of the interviews generated five central themes:

1. Motivation and expectations
2. Prevalence and experience of hearing loss
3. Knowledge of hearing, Audiology and hearing aids
4. Communication
5. Training and future needs

3.2. Motivation and Expectations

People clearly understood that their actions had a direct impact on service users and felt a responsibility to ensure their health needs were met. They took satisfaction in their work when those they supported were happy and content. Many staff spoke of the need to advocate for their service users, regarding health needs. They were aware that it was their responsibility to detect needs for those unable to do so themselves.

Every interviewee was asked to estimate the prevalence of hearing loss in people with intellectual disabilities as a percentage. The median estimate was 25%, although estimates varied from 2 to 80%. A fifth of staff gave responses of 50% or above. However, almost every interviewee said they had only ever known one or two individuals with a hearing loss in their whole career:

I haven’t thought about it. I mean with the people we come across, it isn’t an issue.

111 individuals are supported by staff across these facilities, and at the time of these visits, only eight individuals were known to have some level of hearing loss. This 7% prevalence is below the estimated prevalence of 40% suggesting there was significant undetected hearing loss in this group.

3.3. Knowledge of Hearing, Audiology and Hearing Aids

Not only did people doubt their ability to detect hearing problems, but they also doubted the capabilities of Audiology in achieving an accurate hearing assessment:

To be honest you don't know, cos a lot of our guests wouldn't be able to go through a hearing test.

In addition to doubts around hearing assessment, there was a very negative perception of hearing aids. Every staff member who mentioned hearing aids was critical of them. Not a single positive comment was mentioned.

3.4. Communication

Effective communication was the greatest challenge for staff and was mentioned by all. Staff described a variety of communication strategies, though none of these including hearing.

3.5. Training and Future Needs

Interviewees discussed their preferences for training format and content. Personalisation of training was suggested, particularly activities that involved simulation or experience. There was an overwhelming preference for practical, hands on sessions with group activities. There was no clear preference over whether training should occur within the workplace or at an external location (e.g., a training centre).

3.6. Perception of Audiology

The majority of comments about hearing loss, hearing assessment or hearing aids made by participants were incorrect or misinformed. These included:

- Misconceptions around hearing aids – including who they are suitable for, whistling from hearing aids, and their correct function
- Incorrect belief that people with learning disabilities cannot have their hearing tested or benefit from hearing aids
- Misconceptions around the prevalence of hearing loss

It is not expected of staff to have a detailed knowledge of the different assessment methods available in Audiology, but it is interesting that the assumption is that it would not be possible. If staff hold the belief that hearing professionals would be unable to detect hearing problems, it absolves them of responsibility too. Though there is evidence to the contrary for these assumptions and beliefs (e.g., Coppens-Hofman et al., 2013), the daily experience of caregivers reinforces their perceptions. Viewed in another way, it also suggests disengagement between Audiology and the community. As Audiology professionals we are aware of the wealth of assessment methods and benefits to hearing aid use, but it appears we were not sharing this message with key groups.

3.7. Symbolic Interactionism; A Theory

Symbolic interactionism explains individuals, their actions and the meaning they ascribe to events and interactions. Depending on experiences, meanings can vary between people, but also within a person over time. The behaviour of an individual can change and adapt depending on their environment (Denzin, 1992). This explains why it was important to visit individuals in their workplaces and see how their beliefs were contextualised. In my “environment”, (e.g., a clinic room where individuals are successfully issued with hearing aids), caregiver beliefs about lack of hearing aid benefit do not make sense. However, this is not their environment and the judgements they make about hearing aids reflect their prior interactions:

They are disastrous little things, the noise it makes, it whistles something terrible on occasions

The experience that this participant had when visiting her Father who wears hearing aids has altered her perception. If she began supporting a service user who wore hearing aids who also had trouble with whistling, her prior interaction would affect how she dealt with this issue. If she had already lost confidence in hearing aids, she may approach the issue more negatively, which may affect outcomes for the individual she supported. Kochkin (2007) discovered that successful hearing aid uptake relies on at least 3 events:

1. Recognition of hearing loss
2. Recognition of the problems caused by the hearing loss
3. Belief that the cost of the problem exceeds the cost of the solution

It is therefore clear to see why hearing aid uptake is low in this community. In addition, if staff are supporting individuals with high levels of need on a daily basis and are aware of the difficulties they have in completing basic tasks, they are likely to use this experience to doubt whether hearing assessment would be possible. If they have undergone a hearing test themselves, then their experience of a routine hearing test would further reinforce this belief. Though evidence is available in the literature explaining that alternative hearing assessments are possible, these are unlikely to be accessed by caregivers, who will rely on their own perceptions (Demorest & Erdman, 1994). Because staff spend so much time with those they support, they see themselves as “experts” regarding that individual:

The one person that knows more about these people than anybody is the caregiver because they are with them all the time. If there was a problem we would spot it.

Despite some holding the belief that hearing loss is extremely common, this perception may actually desensitise caregivers to reflecting on the low prevalence of hearing loss in their workplaces. Hearing loss is invisible; a known learning disability is not. This is why diagnostic overshadowing occurs and why staff have difficulty believing hearing loss could be present in someone they know so well (Kevan, 2003). If caregivers are part of a community of practice that as a whole does not encounter hearing loss frequently, this view is reinforced and becomes difficult to break out of, almost like a “script” (Davies et al., 2000). This cultural viewpoint can be difficult to transform (Langer, 1997).

However, social situations are variable, meaning perceptions can change with experiences and time (Foddy, 1994). This suggests any misguided or unhelpful perceptions can be modified. Just as a long term smoker reluctant to stop smoking, may suddenly cease following a close friend's diagnosis of lung cancer, experiences can alter meanings for people if they are relevant and relatable to their circumstances. This first cycle suggested that because the daily working practice of caregivers was not sufficient to change their perceptions, an experience would need to be created, and this was the focus of Cycle 2.

4. CYCLE 2 – DESIGNING AND PILOTING A SOLUTION (SEE MCSHEA, 2015)

The first cycle of this research revealed a low prevalence of known hearing loss of only 7% (compared to an expected prevalence of at least 40%). The caregiver interviews also uncovered misconceptions towards hearing aids, often brought about by family (rather than work) experience. Despite this, staff generally appeared to be motivated not by financial incentives, but by supporting people with learning disabilities. They engaged with training that they felt was necessary, though this did not include hearing.

It became clear that staff were unconsciously incompetent i.e., they would benefit from learning about audiological issues, but were unaware of this need. This is partly due to their environment and interactions, as explained by symbolic interactionism. The solution to the problems identified would therefore be to make staff competent in audiological matters by giving them knowledge and changing their perspectives. Dennison & Kirk (1990) suggest the first step should be to raise the consciousness of staff, to create a desire to learn. A method of learning would be required which not only increased knowledge, but changed perspectives.

4.1. Traditional Approaches to Learning

Historically, learning has been “teacher focused”, where information was delivered didactically, and knowledge was based on subject only (Dennison & Kirk, 1990). This conditioning approach viewed people as machines, who could be programmed (Horwath & Morrison, 1999). However, the shortcomings of this approach were realised and the classic curriculum was transformed to include elements such as a student-centred focus (Warner Weil & McGill, 1989). Terminology changed to shift emphasis from “teaching” to “learning” to reflect this. Learning came to be recognised as a social construction (Seely Brown & Duguid, 1991), a continuous process involving experience (Kolb, 1984).

In the traditional view of teaching, students were passive and had no active participation (Dennison & Kirk, 1990). This meant their cognition, beliefs and past influences were not accounted for. It is clear to see how difficult it would be for some students to engage with learning on a deep or personal level, if their thinking did not align closely with their teacher. A traditional approach suggests that as long as a teacher has expertise in their field, student learning is inevitable (Horwath & Morrison, 1999). This would not have been a suitable solution for training of the caregivers in this study and would have gone against the collaborative nature of the action research methodology employed. An alternative method of

learning was required, in order to appreciate and encourage the experiences and participation of all involved.

4.2. Experiential Learning; an Alternative Approach

Warner Weil & McGill (1989) explain that experiential learning is not only a framework, but also a philosophy. Experiential learning is also known as action learning, so the parallels between it and action research are clear:

Experiential learning is a client focused, support approach to individual group and organisational development, which engages learners, using the elements of action, reflection and transfer

Beard & Wilson (2002, p1)

Experiential learning is said to be one of the most effective methods for adults (Burnard, 1989), particularly as it involves peer-learning (Evans, 1994). Evans also advocated the use of experiential learning for individuals discouraged by formal education. Social care workers are recognised as generally being low-skilled with few prior qualifications (Philpott, 2014b), suggesting formal education did not engage them fully. By approaching transmission of knowledge in a more learner centred way, it was hoped caregivers would become involved in the learning process (Evans, 1994).

As well as providing benefits for learners, there is also the expectation that the trainer gains something (Dennison & Kirk, 1990). Rather than being present as a traditional teacher, the role of the trainer in experiential learning is not neutral in terms of values and feelings (Horwath & Morrison, 1999). This brings an authenticity to the learning experience and helps to make learners feel this is a shared venture. This also aligns with the aims of action research methodology and the dual thrust in this work to increase caregiver knowledge and develop the role of the Audiology professional.

4.3. The Kolb Cycle of Experiential Learning (Kolb, 1984)

- Concrete experience
- Reflective observation
- Abstract conceptualisation
- Active experimental

Kolb's model is arguably the most popular model of experiential learning (Philpott, 2014). Other learning cycles exist, many summarised by Juch (1983). Most alternatives are four stage cycles like Kolb's, using similar themes (e.g., doing, sensing, thinking, addressing). Kolb's cycle provides a framework for the integration of education, work and personal development (Zuber-Skerritt, 1992). It highlights four different aspects of experiential learning which together provide the link between theory and practice, through the use of reflection and action (Burnard, 1989).

Kolb's model has been subject to some criticism, describing it as too simplistic (Jarvis et al., 2003), with no recognition of tacit knowledge (Moon, 2004). Knowledge has social and emotional influences, which are also not acknowledged (Eraut, 1994). However, it is a useful tool to describe the process of effective learning. Often experiential learning is misunderstood, as it is wrongly assumed the experience itself will translate to learning (Evans, 1994). Kolb's model clearly demonstrates the cyclical process required for effective learning.

4.4. Experiential Learning in Practice

The caregivers interviewed in this research expressed a preference for learning which incorporated group activities and practical elements. Previous training that had been memorable to them included simulation and emotion. An experiential approach should therefore be appropriate and effective for this group. It has also been recommended in the literature for staff development through action research (Zuber-Skerritt, 1992).

There is no evidence of experiential learning of this nature in the literature between caregivers and Audiology. This training was designed to be more than basic information sharing. It involved evoking a change in practice through the use of reflection and action. There are people in the community with undiagnosed hearing loss that are being missed through diagnostic overshadowing. The best way to reduce the effect of diagnostic overshadowing is to make people familiar with hearing loss by simultaneously increasing knowledge and their emotional exposure to it. The findings from Cycle 1 suggest that exposure to people with learning disabilities and hearing loss in the workplace alone is not sufficient. Therefore, the experience has to be provided through experiential learning methods. With regards to hearing aid perception, the training must go beyond teaching people simply how to look after hearing aids. It must change their attitudes to hearing aids, increase their confidence and pre-empt problems that can and do occur.

4.5. How Training Took Place

Six residential care facilities were involved in this cycle. All provide care and support to people with learning disabilities. Arrangements were made to visit each facility and provide training at a time convenient for them. It has been suggested that training should occur in the workplace to increase relevance (Purcell et al., 2000; Windley & Chapman, 2010) and promote authenticity of the material being delivered (Eraut & Hirsh, 2007); i.e., "situated learning". All training materials were brought to each home; staff were not asked to contribute or prepare anything prior to training. It was requested that as many staff be released as possible. Group processes are thought to be a rich resource for experiential learning to take place (Warner Weil & McGill, 1989). Each session included 5 – 10 individuals, though evidence suggests group size and duration of training is of no consequence (Lillyman & Farquharson, 2013). Training sessions lasted around 2 hours

minimum, depending on the number of additional questions asked. Training always occurred in the dining rooms of the houses as this was the most appropriate environment in terms of size and seating.

The training was designed to fulfil three aims; to increase knowledge and to change attitudes, with a view to long term change to practice.

4.5.1. Aim 1 – Increase Knowledge

There is evidence in the literature to suggest that training programmes can be successful in increasing the knowledge of participants (e.g., Kyle et al., 2009). And this is a basic, but vital initial aim. In general, Cycle 1 revealed that caregivers are unable to detect hearing loss in those they support, and are largely unaware of the high prevalence. They also had very limited knowledge of hearing aids. In part, training must educate staff around these basic principles.

Much of the hearing aid training was practical and hands on, where each participant was given their own hearing aid, batteries and cleaning materials to work with. Use of objects is often a feature of experiential learning (Beard & Wilson, 2002). This endorsement of practical skills increased authenticity (Eraut & Hirsh, 2007) and helped participants to integrate theory and practice (Seely-Brown & Duguid, 1991).

4.5.2. Aim 2 – Change Attitudes

One of the most important findings of Cycle 1 was the number of individuals who believed hearing loss was common in people with learning disabilities, and then asserted that no individuals they had ever supported had hearing problems. These individuals had accurate knowledge, but were unable to apply this in their working environment. The second aim of the training was to change attitudes; to convince staff that their viewpoints were incorrect and that they were looking after individuals who did have undetected hearing problems.

How can this be done, if their real-life experiences are not enough? As Repper and Breeze (2007) comment, caregivers own exposure in daily work does not seem sufficient. A change in attitude is less likely to occur in traditional methods of learning and instead requires personal engagement (Borbasi et al., 2008). Therefore as well as providing knowledge, the training also needed to evoke emotional responses for deeper learning (Ashmore & Robinson, 2015). However, it was important that these emotions were harnessed in a positive manner. If not engaged correctly, emotions could block learning (Moon, 2004). For this reason, rather than directly challenging the practice of participants, artificial experiences were provided, which would still have the required effect.

Key Element of Aim 2 - Stories and Storytelling

Storytelling is a powerful tool and facilitates emotional learning (Fairbairn, 2002). Real life examples were used as much as possible throughout the training in order to bring life to the principles being discussed and to encourage person centred care. Rather than abstract principles, stories align with how people think and make sense of experiences and as such they reinforce understanding (Ashmore & Robinson, 2015). They provide a safe environment for staff to challenge poor care, make mistakes and reflect on their own practice without feeling vulnerable (Price, 2013). Storytelling is a powerful way of sharing tacit knowledge, which is often overlooked in traditional training (Eraut & Hirsh, 2007).

The activity “Steven’s Story” proved particularly emotive for staff in the training. Steven was a fictitious individual living with a hearing loss, and when the story was told from his point of view, this seemed obvious. It was also having a very negative impact on his life. When the story was retold from his caregiver’s perspective, staff were shocked at her attitude and beliefs, as she felt he had no hearing difficulty and had explained away the signs of hearing loss he presented. By asking staff to write a positive end to the story, it heightened their experience (Fairbairn, 2002). As a result of the activity (an external experience), many staff then began to discuss real individuals they support and draw parallels. It prompted honest discussions about misconceptions, misunderstandings and a realisation that there were perhaps individuals being supported by staff who were living with undiagnosed hearing loss, which then evoked an internal emotional experience (appresentation; Moon, 2004).

4.5.3. Aim 3 – Long Term Change to Practice

This aim is arguably the most important, as it is the one that remains unsolved in the literature and frequently discussed as a need (e.g., Windley & Chapman, 2010; Chadwick & Joliffe, 2008). As part of this aim (and the model of experiential learning adopted), it was important to provide opportunities for reflection on assumptions and expectations as this should lead to more permanent transformation (Koski et al., 2010).

Reflective learning occurs when the internal experience of an individual is challenged (Moon, 2004). The storytelling and emotional activities were designed to do this by changing attitudes. Individual reflection provides an opportunity to challenge thinking in relation to factors such as society and culture which then transforms the reflection into something outward looking (Ashmore & Robinson, 2015). It is then hoped that change to practice will result from a deep examination of attitudes and beliefs (Lindsey, 2002). Reflection encourages participants to take a holistic view and provides a sense of ownership of the learning (Moon, 2004), again important in promoting sustainable change to practice.

Key Element of Aim 3 - Pledges

Though courses can result in effective learning, often the knowledge acquired is not translated to practice as the contexts of the training and work environment are too diverse (Moon, 2004). Though training was conducted in the work environment to promote authenticity, pledges were also used to make the application to working practice explicit. At the end of each session, staff were provided with a piece of paper entitled “I will make a difference” and were asked to write their own pledges. This helped to view the issue as a “shared difficulty” between individual and staff (Pryce & Gooberman-Hill, 2012). It also served as the first step to a longer term commitment. Photographs of staff were taken at the end of training sessions holding their pledges, and were used to create certificates of training.

Staff were keen for follow up visits to be arranged in order to observe their progress. This highlighted their self-confidence (Kyle et al., 2009), in an area they had previously admitted to feeling unconfident in. By organising these follow up visits, it also created adjustment time and a chance to apply their knowledge practically, time which is not always allocated in learning (Eraut & Hirsh, 2007).

5. CYCLE 3 – EVALUATING THE SOLUTION (SEE MCSHEA, 2015)

The purpose of this cycle was to reconnect with caregivers after the training sessions and assess the impact of the training, not only on their working practice, but also regarding their experiences since. Changes to knowledge and attitude are relatively worthless if there is no change to practice, but this transformation of practice can be difficult to measure (Hodkinson & Issitt, 1995). At the end of all training sessions I asked participants the question “how will we know if we have made a difference?” Independently, each home offered the same solution; to do a follow up visit to observe the changes made. This seemed a sensible and positive option. Each home chose when my re-visit would take place. This was important as it should not have been something imposed on them and had to be something they thought was realistic.

In order to reduce the likelihood of initiative decay (Firth et al., 2008), certificates were sent to each home at the half way point between training and the re-visit. Certificates included a photograph of staff teams holding their pledges and a list of all of the pledges made per home to act as a reminder and reinforce learning. This also acted as a small reward which has been suggested as a useful incentive in training and follow up (Stewart et al., 2009). Arrangements were made to revisit homes at a convenient time, where staff who had been part of the training would be available.

5.1. Focus Group Discussions

Group discussions were held with all available staff at the time of the visit, including staff who had not been trained. It was important to include such staff in these discussions, not only to ensure they did not feel excluded from the process, but also as their views were important, regarding inclusion and dissemination of knowledge. Patton (2015) describes focus groups used in this manner as “evaluation focus groups”; providing participants with opportunities to share their perspectives and experiences with specific interventions.

Consent forms were completed by all participants and recordings were made of all discussions. Each discussion began by reminding staff of the pledges they had made at the end of their training session and asking staff to verify whether they felt each one had been achieved or not, with reasons/ evidence in either case. This activity revealed that 96% of the pledges made had been completed and in many cases, were able to provide evidence to verify this. However, staff sometimes found it difficult to verbalise examples. By discussing issues in more detail in each group, a deeper insight was gained. Audio recordings facilitated transcription and thematic analysis, which was carried out in a similar manner to Cycle 1. Codes identified in the thematic analysis were collapsed into central themes:

- Knowledge creation
- Translation to practice
- Empowerment and confidence
- Experience of primary care

5.2. Knowledge Creation

Some staff admitted they had not appreciated how common hearing problems were in this group. They spoke about feeling more aware and having more understanding of hearing issues. They were more knowledgeable about wax management and the process of requesting a hearing test for a service user. Staff were surprised to learn how complex hearing is, and that responding to some environmental sounds, does not necessarily mean speech sounds will be heard. It was clear that on a basic level, staff had learnt something. But what was also evident, was that they were using this knowledge to reflect on previous practice and make sense of it:

We were trained to think about it more, that it's not just the learning disability, they aren't just ignoring you. It's not just them.

When we ask X if he wants a cup of tea, he claps and gets excited but now we think it's not because he hears us, it's because he has seen the cup.

5.3. Translation to Practice

Language like “thinking again”, “now” and “think more” were repeated often to replace the “habit” and “routine” of previous practice. One person even described post training as “a new chapter”. They looked at individuals with a fresh perspective and began to see behaviours and actions in a different way, now considering the possibility of hearing loss. This made them question not only the hearing ability of their service users, but also their previous practice. Staff applied the principles learnt in training to their workplace and the people they support.

And we're now looking at the other ladies, it's making us think “is it their hearing?”

When they are watching the telly we can't tell, we take them to the pictures, we have no idea if they can hear it. I've been here five years and it's never crossed my mind before.

As well as enabling staff to rationalise their past actions, their fresh understanding provided a platform to transform this knowledge into action. Steps have been taken in some of the homes to improve communication by adapting the home environment. Using tactics such as reducing background noise, speaking clearly, and supporting speech with visual cues were all mentioned. Staff also felt these actions could be transferred to other facilities and one person spoke about solving a problem with a hearing aid when they were on cover, only possible with knowledge gained from the training.

Several individuals had been supported to attend GP appointments post training, where no attendances were planned prior to this. Some have needed treatment for wax occlusion or infection and others have been/are in the process of being referred to secondary care for further assessment. Every individual referred so far has been found to have some form of health need. Knowing the range of techniques that were available in secondary care, gave staff confidence to make referrals they would not have considered previously.

5.4. Empowerment and Confidence

Staff reported confidence from the training, because they could watch and copy someone qualified handling a hearing aid and this reduced fear around making mistakes or breaking the device. A major theme in the focus group discussions was around staff feeling more confident in detecting hearing difficulties and more empowered in seeking referrals:

Before I would have thought "oh the GP is just going to turn us away", but now it's better 'cos we have some information to go with.

Caregiver confidence was increased for two reasons; not only feeling more knowledgeable about the subject and the pathways available, but also knowing I was available as a contact who could provide support. Each focus group was next asked to provide estimates of the number of individuals they believed to have a hearing loss before and after training:

	Total	Visible to Audiology
Suspected hearing loss prior to cycle 2	23%	4%
Suspected hearing loss after cycle 3	54%	31%

The perceived prevalence of hearing loss has more than doubled across the six homes. Though these are caregiver estimations (meaning the actual percentage pre and post training may not be entirely accurate), it does highlight an increased awareness. The percentage of those actually known to Audiology could therefore be seen as the translation of knowledge to practice and evidence of a functioning referral pathway.

As a result of the training, several individuals have been referred and supported to access Audiology. Each one has been diagnosed with a significant hearing loss. Certainly for these individuals, change has been achieved. However, if staff now believe that 54% individuals in their care have a hearing loss, why have only 31% been referred to Audiology? Staff admitted that in some cases they had not acted on their suspicions and were yet to make a GP appointment. By maintaining contact with caregivers, it may be possible to facilitate referral for more individuals in the longer term. However, I was also made aware of several instances where referral to Audiology was refused by primary care.

5.5. Experience of Primary Care

It appeared that some GPs may lack the knowledge the caregivers now have. What is surprising (if true), is that any individuals were refused a referral. This questions the manner and nature of annual health checks performed in primary care (where hearing should be included). It also questions the knowledge and attitude of primary care professionals. As one staff member explained, it portrays an image of an uncaring, unethical health service, which does not have time for people with learning disabilities. The training was designed to preempt some GP reluctance (based on my clinical experience), but did not predict those who would refuse to refer outright. In order to investigate caregiver concerns properly, a fourth cycle of research was completed.

**6. CYCLE 4 – INVESTIGATED AN UNEXPECTED ISSUE
(SEE MCSHEA, 2015B)**

This cycle was unplanned and occurred in response to caregiver concerns mentioned in the previous cycle. This highlights the reactive strength of an action research approach. Though there is minimal literature for hearing loss and people with learning disabilities accessing primary care, there are publications which stress the need for an exploration of primary care’s knowledge and attitudes towards hearing loss in older people and the barriers faced (e.g., McCullagh & Frank, 2013). This suggests this final cycle is timely and necessary across Audiology and may help to improve communication and visibility.

6.1. Requirements

Not all caregivers mentioned difficulties in securing referrals from GPs. However, it would be unethical to seek out the GPs in question and interview them. Instead, mailings were sent to all surgeries within Sunderland Clinical Commissioning Group (n = 53) and seven surgeries accepted the invitation to participate. One possible limitation of this approach may have been that smaller areas of poor practice would remain undetected, due to the reliance of practitioners to volunteer themselves to participate. If anything, this method of recruitment should encourage the best practitioners to come forward. It could be argued therefore, that some of the negative findings of this cycle are even more poignant. None of the GP surgeries mentioned by caregivers in the previous cycle volunteered to participate in this cycle.

Individual, semi-structured interviews were chosen, conducted and analysed in a similar manner to Cycle 1, to promote consistency of method. The interviews in this cycle involved practice nurses and GPs. An individual approach encouraged more honest responses (Bryman, 2016), given the potentially sensitive nature of the questioning i.e., sub-optimal care for people with learning disabilities. Pragmatically, individual interviews were also the most feasible option as most surgeries were only able to spare one staff member due to clinical pressures. In this cycle, the questions that were asked were informed by the previous cycles. For example, some caregivers had suspicions that people with learning disabilities would be treated differently to adults in the general population.

It appears that the concerns of some caregivers in the previous cycle were founded. It is interesting to compare the prevalence data provided by primary care professionals with the caregivers at an equivalent stage:

	Median prevalence estimate	Prevalence actual
Caregivers at interview phase (Cycle 1)	25%	7%
Primary care staff at interview phase (Cycle 4)	20%	0-14%

The findings for primary care, like caregivers in Cycle 1, may be explained in part by symbolic interactionism (that in primary care few people with learning disabilities actually present with hearing problems, therefore the perceived prevalence reflects this).

Practice nurses had little knowledge of Audiology; they felt their expertise lay in general health and health promotion. However, referrals from GPs were also rare due to assumptions and judgements being made. Mencap (2012) stress the need to challenge such assumptions and ensure consistent care, regardless of a learning disability. The GPs interviewed felt confident making referrals to Audiology when adults in the general population presented with hearing concerns. They relied on history taking, ear examination and the need for active concerns from the individual or their caregiver. This is a high referral threshold for people with learning disabilities. Some may not tolerate a physical examination, or may not be able to provide a detailed medical history. Often the caregivers that accompany individuals or not able to provide this on their behalf. In many cases a GP may only refer on the basis of active concerns, which is unlikely to be the case for this group, due to diagnostic overshadowing. In general practice it may not be common place to look for problems that are not causing concern, but this is the purpose of the annual health check, to redress the disparities people with learning disabilities face. There seemed to be a misunderstanding that something causing concern would always be visible. This is not always the case for people with learning disabilities.

However, there is also evidence to suggest that even if a caregiver does present an active complaint on behalf of an individual, this is not always acknowledged or acted upon (Ali et al., 2013) and that even for adults in the general population, around 45% of individuals are not referred to Audiology when presenting with hearing loss (Action on Hearing Loss, 2011). The reasons for this are said to include time constraints, lack of awareness of assessment or benefits to rehabilitation (Schneider et al., 2010).

Some individuals felt that hearing loss was rare, or had already been dealt with for individuals they saw in their clinics. Others felt that for this group, addressing hearing loss was not a priority, as it was unclear how an individual's life would improve following treatment. Some believed that it would not be possible to assess hearing accurately or even facilitate attendance at an Outpatient clinic. Using this model, it becomes clear that simply improving caregiver knowledge is not sufficient to transform the whole cycle. Though improved caregiver knowledge may highlight to primary care that a problem does exist, it does nothing to transform its perceived importance, or availability of solutions.

Audiology has a responsibility to share the positive outcomes that can stem from treating hearing loss, not only from a personal perspective, but also a financial one. By publicising the Audiology service and the reasonable adjustments it can provide, this would help to influence referrers. Locally it was disappointing to hear staff say they thought there would be no one in Audiology "who would care" about people with learning disabilities, when there has been a dedicated service in place for 7 years. This reinforces the invisible nature of Audiology but also highlights the need for this issue to be viewed with shared responsibility.

7. DISCUSSION

The issue of improving audiological care for people with learning disabilities is complex and involves a variety of stakeholders. There is clear evidence of poor audiological care within Audiology literature, but limited dissemination of the message to those impacted by it. There is also little reflection on the responsibility of the profession. This research was more

about understanding the role and influence of an Audiology professional, than simply educating caregivers.

7.1. Contextualising the Findings

Cycle 1

The findings from this cycle agree closely with the literature. The 7% prevalence of hearing loss known to the participants reinforces the findings of Kerr et al. (2003), who suggested that caregivers have difficulty detecting hearing problems. There was evidence of diagnostic overshadowing in this research group and agreement with McMillan et al. (2000) and Pryce & Gooberman-Hill (2013) that knowledge of hearing issues obtained by work experience alone is not sufficient. In contrast, it appeared that caregiver experiences actually reinforced their misconceptions. Negative judgements were made regarding hearing aids and their benefit. Coppens-Hofman et al. (2013) also found the benefits of hearing aids were under-reported and believed this was due to lack of initial concern regarding hearing.

This research explores the issue further and aims to provide a theoretical explanation for these findings, using symbolic interactionism (Denzin, 1992). The unconscious incompetence of staff, their prior experiences with hearing aids and the lack of visible hearing difficulty in the people they support, has led them to construct meanings which justify low prevalence of hearing loss, regardless of their estimates of general prevalence. They are not surprised when they do not encounter individuals with hearing difficulty, and so the cycle of unconscious incompetence continues. Though they were aware of their responsibilities in advocating referral for services users, their experiences suggested this was not something that was required frequently or would be successful if attempted.

The theory of symbolic interactionism suggests that although individuals form their own meanings based on experience, these can also be transformed by experience (Denzin, 1992). This suggests the issue could be improved. Teamwork and involvement were important to staff and it became clear they would engage with collaborative methods. Though this has been suggested generally in the literature, there was no evidence of an attempt to do this between caregivers and Audiology. Action research methodology was integral to this, and allowed caregivers to make suggestions about training which were integral to the next cycle.

Cycle 2

Though further training and education is frequently mentioned (e.g., Lennox et al., 1997; Tracy & McDonald, 2015), there have been no real attempts to demonstrate a translation of knowledge to practice, particularly for hearing loss and people with learning disabilities. In order to determine whether this was possible, it was necessary to provide caregivers with a novel learning opportunity. Traditional teaching methods are successful if the thinking of the student and teacher align. However, there is evidence in the literature to suggest caregivers often feel ways of working are imposed on them, by people who do not understand their role (DH, 2007). This may explain why simply relaying knowledge between two groups is not successful, as there is no context to the information. For example, McMillan et al. (2000) successfully increased the knowledge of their participants, but were unable to demonstrate a convincing transformation to practice.

This was the justification for designing training in this cycle using experiential learning theory. This requires opportunities for reflection, with the aim of evoking change. Seely Brown & Duguid (1991) describe this as the difference between learning to become a practitioner, and merely learning about practice. During both Cycles 1 and 2, participants were encouraged to offer ideas and suggestions in order to reach a common understanding, leading to agreed action. Again this appeared to be a novel approach in the Audiology / learning disability literature. In addition, by situating the learning within caregivers' workplaces, it made the learning authentic and promoted translation to practice (Borich, 2011). This also provided me with a novel opportunity to visit these homes and experience the culture and daily practice. This was important to reflect upon and provided an opportunity for some situated learning of my own.

Cycle 3

As this approach was novel, it is difficult to contextualise the findings of the evaluation of the training with other studies in the literature. Though there is agreement that translation of knowledge to action is difficult (e.g., Windley & Chapman, 2010), there has been minimal research to understand the reasons for this (Eraut & Hirsh, 2007). Hithersay et al. (2014) agree, that more research is required to understand how best to engage caregivers. In this regard, the findings of Cycles 2 and 3 add to the evidence base. Experiential learning was a successful approach for these caregivers, and there was evidence to suggest all three training aims were met. On the whole, knowledge and confidence increased as shown by questionnaire. A focus on storytelling was important in facilitating reflection that is integral to experiential learning. This assisted in changing attitudes around hearing loss. Participants also mentioned the value of having a known contact in Audiology, and the reassurance that they had support in specialist services. This led to focus groups reported increased confidence and empowerment. Such caregiver support was one of the key findings of this cycle and was also cited by Ali et al. (2013) as important in general healthcare.

Caregiver estimations of hearing loss prevalence increased significantly from 23 to 54%, which correlates more closely with the expected prevalence reported in the literature (40%; Emerson et al., 2012). Though these are estimations and may not be entirely accurate, caregiver estimations are used more frequently in the literature to comment on prevalence than actual assessment (Bent et al., 2015). In this research, further investigations were made involving actual diagnoses known to Audiology. Four individuals were diagnosed with hearing loss following this cycle, with caregivers in these homes admitting that it was unlikely these hearing losses would have been identified or actioned without the training they received. Many other caregivers began using better communication tactics with those they support. This suggests people with learning disabilities benefited as a result of the process. Horwath & Morrison (1999) state that this is the most effective test of knowledge transfer.

There was evidence to suggest that more individuals are now suspected of having hearing loss than have actually been referred. Whilst the lack of referrals was partly due to caregiver inertia, there was also suggestions of barriers in primary care. Firth et al. (2008) voice the concern of oversimplifying an issue to simply a problem with caregivers and the findings in this cycle and the next would support this concern.

Cycle 4

This final cycle occurred through identified need rather than prior planning, highlighting the reactive strength of action research. The findings of this cycle suggest that the concerns raised by caregivers previously were founded and widespread. Despite evidence that health checks in primary care are generally effective (Robertson et al., 2010) this research agrees with McClimens et al. (2014), who assert that this is not the case for hearing loss. These authors suggest further evaluation is needed, which this research helps to provide. The prevalence data obtained from surgeries reveals inertia in primary care, similar to that observed in Cycle 1 with caregivers. Many of the primary care professionals involved made negative value judgements about the worth and benefit of treating people with learning disabilities and their hearing difficulties. Even for some, where a hearing loss was documented in their medical records, referrals had still not been actioned. This echoes the findings of Felce et al. (2008), where health checking did not lead to increased contact with specialist services.

This cycle found that GPs needed three key elements in order to feel confident in making referrals to Audiology; physical examination, history and active concerns. One or more of these elements may be more difficult to obtain for people with learning disabilities, highlighting the importance of a familiar and knowledgeable caregiver (Lennox et al., 1997). However, the account of some caregivers in Cycle 3 suggested that their active concerns were not being acted upon. This is not a finding unique to this study and had previously been described in more general terms by Mencap (2012). It appears that on some occasions, improved caregiver knowledge alone was insufficient to achieve a referral to Audiology services. The perceived importance of hearing well and the availability of a solution to hearing loss for people with learning disabilities was still under suspicion by some primary care professionals. Staff in primary care had limited understanding of the patient journey within Audiology, also highlighted by Monitor (2015). It was disappointing to hear so many professionals say that there was no local audiological provision for people with learning disabilities, when a service has been in place in their local area since 2008. What became clear was that the visibility of the Audiology service, and the referral mechanisms to access it must be improved.

Though caregivers were the focus of the first three cycles, the findings in primary care could be considered even more significant. Where caregivers are not considered to be professionals and their mandatory training does not prepare them adequately for detections of hearing problems, primary care practitioners are professional and have explicit responsibilities towards meeting the health needs of their patients, including hearing. The fact that their prevalence estimates fell below those of the caregivers is a concern, particularly when coupled with some poor attitudes regarding people with learning disabilities.

7.2. What were the Key Elements in Ensuring the Research Aims were Met?

Rather than focussing on determining an absolute value of effectiveness, it is more important to determine *what* was effective. Although the content of the training was important, it appeared more significant that I was physically available to caregivers. The key elements that caregivers required were:

- Knowledge that hearing loss is more common in people with learning disabilities
- Assertion that hearing problems can and should be addressed
- An explanation of the referral process

The training content helped to provide legitimacy to the issue. The use of situated learning and experiential learning meant the training was designed to make these issues interesting, memorable and relevant. Meeting an Audiology contact who spoke about these issues personally, made caregivers feel empowered and confident. Vygotsky describes this as a “scaffold” of support, where caregivers could feel supported and encouraged to learn and develop (Borich, 2011). It meant that the caregivers were more observant for signs of hearing loss in those they supported, not only because they were educated in what to look for, but also because they knew there was something that could be done. It could be argued that caregivers should not need to retain advanced hearing knowledge, only that they know who to seek this information from. The only real health contact caregivers have in the community is primary care, and the final cycle of research suggested that in many cases, primary care has the same needs as caregivers. The common denominator in this is Audiology, which has a professional responsibility to increase its visibility in the community.

7.3. A Multidisciplinary Team (MDT)

Traditionally, professions have become specialised, resulting in a narrowing of vision (Schön, 1983). This narrowing can affect the experience and understanding of individuals to an extent where perceptions become fixed, almost like a “script” (Davies et al., 2000). This viewpoint can be difficult to transform (Langer, 1997) and perhaps unlikely to transform spontaneously, without external influence.

Heyman et al. (2004) feel that specialisms are still required for people with learning disabilities and that secondary complexity can arise when standardisation of services is attempted. A more effective solution therefore, is to adapt the processes between specialisms and work together. Owens et al. (1995) describe the differences between multi-professionalism (retaining specific knowledge but working across boundaries) and inter-professionalism (surrendering work roles and integrating procedures). Multi-professionalism is the less disruptive and therefore most feasible option. For hearing loss in people with learning disabilities, with such diverse stakeholders, it would be difficult to imagine true inter-professionalism.

By working with stakeholders in the community, the benefits to Audiology are clear. It provides an opportunity to communicate with the key gatekeepers to its service, not only to encourage appropriate and quality referrals, but also to address any barriers or issues that may not be obvious within the profession. For example, prior to commencing this research, I was unaware how negative the community perception of hearing aids was. This may help to explain why, although hearing aid technology has improved hugely, uptake of hearing aids has increased less so (Kochkin, 2007). By learning this in Cycle 1, it allowed me to design training which could change attitudes. Without this feedback, the training would not have been tailored as effectively and may therefore have resulted in a less favourable outcome.

7.4. Audiology's Visibility within a Multidisciplinary Framework

It is believed that assessment and management of hearing loss should be multidisciplinary (Miller & Kiani, 2008). It is therefore even more surprising to consider the omission of Audiology when hearing issues are being discussed. This appears to be a widespread issue, and is a concern if Audiology is not associated with hearing. For example, Lindsey (2002) writes about the range of professionals required to meet special health care needs in people with learning disabilities. She acknowledges the increased risk of sensory impairment, but discusses this in relation to the responsibility of speech and language therapists only. The National Institute for Health and Care Excellence (NICE) produce guidance on improving health and social care. There is only one document which mentions hearing issues for people with learning disabilities (document reference CG142; for adults with autism). Though hearing tests are mentioned, there is no reference to Audiology.

Similarly, Newsam (2010) asked caregivers who they would approach for advice on sensory impairment. Opticians, GPs and even a charity for those with visual loss were mentioned; though there was no mention of Audiology whatsoever. Though vision and hearing share many parallels, there are significant differences in perception. Glasses are more socially acceptable, often perceived as a fashion accessory or a sign of intelligence. Whilst people can self-refer for a sight test, the process of obtaining a hearing test relies on primary care and therefore creates distance between the public and Audiology.

There is also evidence in the literature to suggest that Audiology is infrequently recognised as part of a wider team. A key example is MacDonald et al. (2010). This was a case study highlighting the outcomes for an individual regarding behaviour support planning to reduce challenging behaviour. Although he did not communicate verbally, had limited understanding of speech, found noisy environments difficult and did not like group situations (all key indicators of hearing loss), there was no attempt to test his hearing, nor was there mention of hearing issues in the whole publication. The inclusion of Audiology and a potential diagnosis of hearing loss could have led to a very different outcome for this individual. The case study presented in McShea et al. (2014), highlights this and the significant benefits inclusion can bring, not only for the person concerned, but also financial benefits for services.

7.5. Creating an MDT for Audiology and People with Learning Disabilities

Benefits to Caregivers

A multidisciplinary approach is needed to allow Audiology, caregivers and primary care professionals to come together to best support people with learning disabilities and hearing loss. This research has demonstrated that increasing contact with caregivers can influence their practice in a productive manner.

Time pressure is already a feature of caregivers' practice, so involvement in a new initiative may be met with some resistance. However, the high prevalence of hearing loss in people with learning disabilities, justifies the need for such an initiative (Meuwese-Jongejeugd et al., 2007). By working together, pathways can actually become more cost and time effective. For example, if a caregiver had concerns about the hearing of an individual

they supported, they may have had to support the individual to their GP on several occasions before a referral was processed (if at all). By having greater awareness of the multidisciplinary team and its remit, the referral process should be quicker and easier for staff, who would be more informed and empowered.

Working together has also been suggested by Fyson & Cromby (2013) as a way to improve the difficulties created by neoliberal service structures. Though neoliberalism is thought to create choice and opportunity for individuals, it is unlikely to have such a positive impact on people with learning disabilities, who may have difficulty making autonomous choices. Equally, their caregivers may have difficulty making appropriate choices on their behalf, if they are uninformed and unaware. Supported decision making has therefore been advocated, not only in social care, but also in Audiology (e.g., Pryce & Hall, 2014). MDT working can be a vital tool to facilitate this.

Benefits to Primary Care

Schneider et al. (2010) feel the management of hearing loss in primary care is questionable. The findings from Cycle 4 indicated that many primary care professionals held dated beliefs that it would not be possible to test the hearing of a person with learning disabilities or that hearing aids would make no difference to their lives. By having closer links with Audiology, these perceptions would change and would make referral more likely. In addition to this, visibility of a contact in Audiology helps to raise awareness of the issues and referral procedures and could therefore save money. Prior to our engagement with primary care locally, individuals often reached the complex needs service in hospital Audiology after being referred inappropriately to other providers, who were unable to meet their needs. Delivering the right service first time is not only preferable for the individual, but also for commissioners and providers of services.

Benefits to Audiology

For Audiology, an MDT would facilitate increased presence and influence in the community. It would also help to provide feedback on how the profession is represented elsewhere. By being part of an MDT, Audiology would be more aware of issues that affect the profession and would lead to a presence outside of the clinic room.

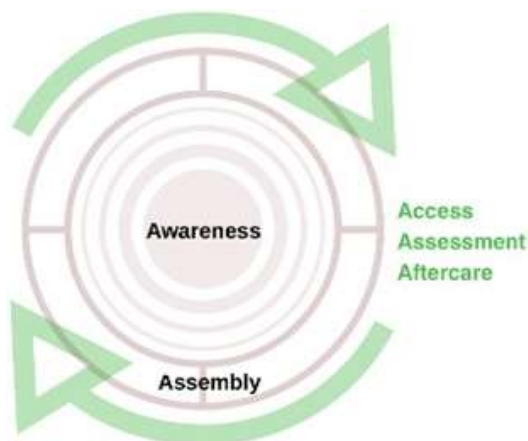
7.6. A Theoretical Model for the MDT

Regardless of the exact organisation and membership of an MDT, the main objectives should be timely detection, access to support and longer term management (Miller & Kiani, 2008). Taken the research findings into consideration, an enhancement to the 3As model is proposed, to transform it into a 5As model with the addition of "Assembly" and "Awareness":

Assembly

One focus of the 5As model is now the stakeholders. There is no minimum or maximum number of stakeholders, this can be determined according to the need and remit of the group.

Initially, an assembly of stakeholders is necessary to consider the issue and determine membership.



Initially, there may be resistance to adopting an MDT approach. Stakeholders may be more comfortable within their own disciplines, which are familiar and predictable (Hills et al., 2007). The assembly should therefore be driven by a stakeholder who is central to the issue and is affected by all other parties. Though this could potentially be the individual or their caregiver, they are unlikely to have the capability or resources to coordinate this. For hearing loss and learning disabilities, Audiology seems to be a valid alternative. Shames & Simpson (2012) suggest Audiology is well placed to be at the centre of patient focussed care. This would also increase the visibility and responsibility of the profession.

Awareness

Once assembly has occurred, awareness should follow. Key contacts could determine roles and capabilities and would streamline the patient journey. By sharing practice, it could be determined who was best placed to act on needs as they arose. It may be that the number of stakeholders involved varies as required. Symbolic interactionism states that individuals construct meaning from their experiences and environment. Multidisciplinary information sharing can be effective in modifying experience and perception.

Once assembly and awareness are in place, the established flow of access, assessment and aftercare could continue and could be conceptualised in a spiral of cycles, rather than one discrete event. By having a robust core of assembly and awareness supporting this spiral, the developments made are more likely to be sustained. This would also mean that initiatives would not rely on individual stakeholders, as there would be shared ownership. By encouraging shared meaning and experience, values would align and mutual understanding would occur. The focus would shift from service centred to person centred.

7.7. Generalisability/Transferability of the Model

It is recognised in the literature that qualitative research is not generalisable at the level of populations, but at the level of theory (Bryman, 2016), meaning the quality of the inferences

to theory are important. For example, Silverman (2013) shows that qualitative research can be classed as generalisable if the findings are presented to demonstrate what groups *can* do, rather than absolute descriptions of what they *actually* do. In this research therefore, rather than looking at the *exact* prevalence numbers before and after caregiver training for example, the findings are more generalisable when considered as the *possibility* of change to practice.

Despite the dual thrust within action research methodology, it is said that the action component is often prioritised over the research component (Dick, 2003). It was important throughout this process to remember that this was a piece of research which intended to generate theory, and was not just a project in practice. It was helpful to use the cyclical nature of the process, which provided natural pauses for reflection, evaluation and future planning. Dick (2003) suggests that theory can be generated in action research by examining the overlaps between the data sets generated by cycles. This is similar to the process of triangulation (Greene 2014), where validation of findings occurs through use of multiple sources. For example in this research, the invisibility of Audiology in community settings was made clear from participants in two separate cycles (1 and 4). It was from overlaps such as these that the 5As model was conceptualised. A model is a framework for examining reality (Silverman, 2013). Therefore, by returning to the earlier point made about generalisability in qualitative research i.e., "can do, not does do" then the 5As model could be classed as generalisable across other Audiology / care providers and wider health and care networks. In addition, as the focus of the 5As model is on groups and organisations rather than individuals, the level and sustainability of change it proposes is maximised (Handy, 2009).

CONCLUSION

I believe this research has made an important contribution to both theory and practice. Through the use of action research methodology, this research can be viewed as a successful educational intervention. I have established that it is possible to increase the audiological knowledge of paid caregivers and facilitate translation of that knowledge to changes in practice. This had not been demonstrated in the literature previously.

Such translation resulted in significant benefits, not only for the caregivers themselves, but for the individuals they support. The lives of some individuals have been transformed as a result. It highlights the need for greater importance to be placed on audiological issues for people with complex needs and a greater awareness of their supporters, advocates and healthcare providers.

This research has highlighted the role of the wider team and other stakeholders through development of a conceptual model (the 5As model) to facilitate multidisciplinary engagement for Audiology.

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Chapter 10

HEARING LOSS AND INTELLECTUAL DISABILITIES

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ABSTRACT

There is a high prevalence of hearing loss in individuals with intellectual disabilities and it can affect communication, personal relationships and mental health. Awareness of this issue is increasing, as is our ability to assess hearing and offer appropriate rehabilitation, however significant developments in audiological care and management are still required and further research needed. This chapter discusses the importance of hearing loss identification and rehabilitation, aimed at professionals across different disciplines and also as a starting point for those new to the audiology profession. Various points on the Audiological care pathway for people with intellectual disabilities are presented including: identification of individuals who require hearing loss investigation, methods of assessment of hearing loss, and appropriate rehabilitation. This chapter includes the challenges faced by PwID and hearing loss and by clinicians. The chapter will conclude with some of the authors' recommendations for improved Audiological care for PwID.

1. INTRODUCTION

Our relationship with sound is personal and unique. The impact that hearing loss has on quality of life will vary enormously depending on the person, but is known to potentially affect communication, education, relationships and mental health. There is growing awareness of the importance of hearing health in the general population internationally;

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however, this issue is still under-recognised for those with intellectual disabilities. In this population, not only is the prevalence of hearing loss greater but the impact on life is too, particularly if not recognized; yet this is little known by those in caring or other health roles. The authors aim to provide a summary of the importance of hearing loss identification and rehabilitation, both for professionals across different disciplines and as a starting point for those new to the audiology profession.

This chapter discusses the points along the Audiological care pathway for people with intellectual disabilities (PwID) including: identification of individuals who require hearing loss investigation, methods of assessment of hearing loss, and appropriate rehabilitation. This includes the challenges faced by PwID and hearing loss and by clinicians. This is drawn from both peer-reviewed and grey literature internationally, with additional recommendations from the authors' experience individually and as part of the UK special interest group for professionals working in hearing and people with learning disabilities, HaLD. The chapter will conclude with presentations of the authors' recommendations for improved Audiological care for PwID.

2. HEARING LOSS

According to the World Health Organization, there are currently 360 million people with disabling hearing loss globally (WHO, 2015). The prevalence varies with country, but to take as an example the UK, hearing loss affects approximately 1 in 6 of the population. Prevalence figures are considerably higher in individuals with intellectual disabilities and higher still with certain syndromes; however, there are significant limitations to this data. This is partly related to the accuracy of hearing tests in the literature - some of the adjustments that should be taken when testing hearing in this client group are often not available. Many authors draw prevalence data from hearing screening programmes carried out at the Special Olympics; this data is restricted to individuals who are usually in good physical condition and often with milder intellectual disabilities, and so possibly not truly representative of the population as a whole. However, Hey et al. (2014) compared the prevalence figures from the Special Olympics with that of the residents of a school for individuals with intellectual impairment and found the 2 sets of prevalence data very similar.

Despite this high prevalence, hearing loss is still not widely recognised. As an example, one study suggested 70% of adults over the age of 40 with Down Syndrome to have significant hearing loss undiagnosed before systematic hearing testing (Van Buggenhout et al., 1999). Possible reasons for this are discussed further below.

2.1. Cause of Hearing Loss

The leading cause of hearing loss in any population varies by country due to factors including general health, genetics and exposure to drugs and noise. One of the primary aims of professionals such as Audiology or Ear Nose and Throat teams, who see individuals referred with concerns about their hearing, is to identify what type of hearing loss they may have. The type of hearing loss will partly determine the most appropriate management, as

there are simple surgical and medical options available for some causes. Hearing losses can be loosely grouped into conductive hearing loss and sensori-neural hearing loss (or a mixed loss, which means there are multiple causes for the hearing loss). This section outlines some of the more common issues that are identified as causing a hearing difficulty in both the general population and those with intellectual disabilities.

2.1.1. Conductive Hearing Loss

A conductive hearing loss is an issue that arises in the outer or middle ear, so reducing the level of sound before it can reach the cochlea (the organ of hearing). A very frequent cause of conductive hearing losses is earwax. Individuals with intellectual disability as a result of a syndrome may have narrow ear canals or dysmorphic ears that restrict the natural passage of earwax. An additional aspect of narrow or tortuous ear canals is that otoscopy (examining the ears visually) may not be achieved, as a clear view of the ear drum may not be possible. Excessive earwax affects approximately 2% of the general population; in the population of individuals with intellectual disabilities it has been found to be in the order of 30% (Crandell & Roeser, 1993; Smith et al., 2000). Long-standing impacted earwax can increase the risk of infection, cause discomfort and result in or increase tinnitus (noises experienced in the ears or head). Its presence will also prevent an accurate hearing assessment. Earwax can be removed using a range of methods, including softening (ear drops) which can be administered at home, and ear syringing, manual removal or micro-suction by trained professionals. For many with intellectual disabilities this is a simple process and, if checked and acted on regularly, can be managed effectively. If a client is tactile defensive, however, other approaches may be needed and working closely with carers may enable the practitioner to provide appropriate adjustments. As standard, hearing assessment appointment letters will often advise ear canals are checked and any wax removed before attending. In the authors' experience, this advice is frequently not followed. A further referral to remedy this, such as to an Ear, Nose and Throat department may be required, increasing the number of visits and length of the care pathway. Foreign objects found in ear canals may also cause hearing loss along with physical risks if not dealt with, and should also be removed professionally.

Beyond the eardrum, the middle ear space should be air-filled, however there are times when it can be filled with a fluid which stays for a long period, commonly known as "glue ear." Glue ear is very common in children. It can also be present in adults, associated with temporary upper respiratory tract infections, but will often drain naturally afterwards along the "eustachian tube" into the back of the throat. There are often surgical solutions to longer standing conductive hearing losses, such as insertion of small temporary tubes known as "grommets" in the eardrums to drain the fluid. This is a simple procedure which may be completed with local or general anesthetic although that brings risks to those with other medical conditions, such as may occur in those with syndromes. Due to these risks, an increasing number of patients with this type of conductive hearing loss are opting for hearing aid use instead of surgery, which will be expanded on later in this chapter. If not treated, there is a possibility that glue ear can cause permanent damage to the ear (Balkney et al., 1979) and consultation with an Ear, Nose and Throat specialist should be sought in the case of longstanding glue ear.

The prevalence of chronic ear infections varies dramatically across the world. According to the World Health Organization (2013) "over 90% of the burden of chronic ear infections is

borne by countries in the south-east Asia, western pacific and African regions, and ethnic minorities in the pacific rim.” In addition to causing a hearing loss, chronic ear infections can lead to other life threatening conditions. In the case of an individual who does not accurately self-report, ear infections are more likely to be identified by family members or carers than other causes of conductive hearing loss because there is often a discharge or smell that can be observed. Also, this is more likely to cause pain than other causes of hearing loss.

2.1.2. Sensori-Neural Hearing Loss

A sensori-neural hearing loss is the catch-all term for hearing losses that affect the “cochlea,” or that affect the “auditory nerve.” Sensori-neural losses are usually permanent with no surgical or medical interventions to resolve them. They can be progressive. The most common form of sensori-neural hearing loss results from damage to the cochlea, however it is estimated that approximately 10% of sensori-neural hearing losses may be due to an “auditory neuropathy spectrum disorder” (ANSD) (Uus & Bamford, 2006). This term is used to describe a combination of Audiological findings which would suggest good cochlear function but pathology of the auditory nerve, distorting the signal travelling to the “auditory cortex” in the brain.

In some countries, for example the UK and the US, sensori-neural age-related hearing loss (presbycusis) is the most common cause of hearing loss; as an example, Action on Hearing Loss in the UK report that the numbers affected increases to over 40% of those over 50 years old and over 70% of those over 70 years old. As human longevity increases, so the prevalence of hearing loss will also increase. An increased prevalence with age has also been observed in the population of individuals with intellectual disabilities. In a recent review of the literature on this topic, Bent et al. (2015) identified studies that reported on hearing loss prevalence with age. The prevalence of hearing loss in adults with intellectual disabilities under the age of 50 was found to range from 27% to 45%, and over 50 years of age from 59% to 68% (Buchanan, 1990; Venhuis, 1995; Evenhuis et al., 2001; Meuwese-Jongejeugd et al., 2006; Van Buggenhout et al., 1999).

2.2. Hearing Loss and Down Syndrome

While there are multiple syndromes which feature hearing loss and an intellectual impairment, Down Syndrome has the highest incidence of hearing loss. The prevalence of sensori-neural hearing loss is higher in this group from birth, and this incidence increases as the individual gets older. Age related hearing loss is not only more common in Down Syndrome but also at an earlier age, often by 20 to 30 years. Three studies looked specifically at the prevalence of hearing loss in individuals with Down Syndrome, due to the associated high rate of sensory issues and precocious ageing. For this specific group under the age of 50, prevalence was reported from 38% to 76%, and for those over 50 years of age, from 62% to 93% (Evenhuis et al., 2001; Meuwese-Jongejeugd et al., 2006; Van Buggenhout et al., 1999).

Appropriate management will be discussed later in this chapter, but it should be highlighted that ear wax is a particular issue for this group as ear canals are typically narrow, so only a relatively small amount of ear wax is sufficient to block the ears.

Additionally, for individuals with Down Syndrome, glue ear is much more common than in the general population, due to a number of factors such as narrower eustachian tubes and

the middle ear fluid tending to be of a different viscosity than in other people, taking longer to drain and more likely to become infected (Sacks & Wood, 2003).

2.3. Hearing Loss and Other Causes of Intellectual Disabilities

There are many syndromes which commonly present with both hearing loss and intellectual disabilities, including Down Syndrome, CHARGE syndrome and Cornelia de Lange. In addition to syndromic causes, there are genetic causes of the co-morbidities of hearing loss and intellectual disabilities, such as chromosomal and mitochondrial disorders. There are also a wide range of perinatal factors that can influence hearing and intellect, including extreme prematurity and congenital infections. Some causes of intellectual disability have specific types or patterns of hearing loss, or other symptoms that are uncommon with other causes. It is beyond the scope of this chapter to provide a thorough discussion of these factors.

Intellectual disabilities are usually present with multi-morbidities, some of which will compound the impact of hearing loss and should also be taken into account when the hearing is being assessed and managed. These are discussed as relevant to each section.

3. ACCESSING AUDIOLOGY SERVICES

Those with concerns about their hearing should seek help in order that any pathology may be addressed, to understand what is causing the difficulties, and to seek rehabilitation. Hearing loss which is not identified or managed can have serious effects on communication, social activity and participation, along with increased risk of depression and dementia (Action on Hearing Loss 2014). It is known that there tends to be a ten year delay in seeking help for hearing in the general population (Davis et al., 2007); it is thought to be worse still in those with intellectual disabilities. This may be in part due to some carers' lack of awareness of symptoms of hearing loss. Also, in the case of adults with long standing undiagnosed hearing loss, if the individual has developed an alternative form of communication that is effective there may be a lack of interest in hearing assessment. Hearing loss is as affected by diagnostic overshadowing as any medical condition, with typical misconceptions being that lack of response to speech or an observed behaviour change is related simply to a person's intellectual disability.

3.1. Referral Pathways

If there are concerns about hearing, the starting point is to identify if earwax is obstructing the ears, given the high occurrence as mentioned above, and the ease of resolving this in the majority of people. Wax is a healthy and normal part of the ear, and should not be 'cleaned out' by the individual or family or carers; cotton wool buds and tips carry a warning in some countries (e.g., UK) due to the risk of puncturing the ear drum and the abrasive effect on the canal wall. Instead, ears should be checked regularly by healthcare professionals in

those with excessive production of wax, or those with ear structure that prevents natural migration of wax out from the ear. Appropriate advice on management can then be given.

However, when the ears are free from obstruction, further consideration should be given to hearing loss in other parts of the ear. It should go without saying that looking into the ears is only a small part of the hearing pathway, and a referral to hearing professionals, such as an Audiology department should follow. The authors' experience is that regrettably it is a widely held – but inaccurate – belief that hearing assessment is not possible with individuals with intellectual disabilities. This belief is likely to be a contributing factor to those with a hearing loss not accessing services. While modifications to standard hearing assessment is often necessary and there may be limitations to the outcomes of such assessments, it is rare that hearing assessment of some form cannot be achieved.

3.2. Screening

A majority of countries in the world now offer universal newborn hearing screening, as this is widely recognized as the optimum time to identify a hearing loss in the general population (Davis et al., 1997), and screening checks available for this age are quick to complete. However, this only identifies a proportion of permanent hearing losses and progressive losses exist, so further hearing screening at later ages is usually recommended. Hearing screening for adults continues to be debated (e.g., Lamb & Archbold, 2016; Pronk et al., 2011). There is arguably a strong case for offering a targeted hearing screening to individuals with intellectual disabilities in adulthood as the prevalence of hearing loss is so high in this population. Also the impact of hearing loss is likely to be multiplicative (Wiley & Moeller 2007). Furthermore self-report may not be accurate for individuals within this group (Emerson et al., 2013). At the time of writing, the European Federation of Audiology Societies is working on recommendations for screening this population (EFAS, 2015).

In the UK, an annual Health Check is offered to some adults with an intellectual disability by their general practitioner, and includes a small section on hearing and communication (RCGP, 2010). Despite the potential that this routine targeted consideration of hearing should bring, the check currently relies heavily on client and carer report, which has been found to significantly under-identify hearing loss (Bent et al., 2015). It has also been suggested of general practitioners' role "Current training is not sufficient to provide the skills for detection and management of hearing problems" (McShea et al., 2015).

3.3. Suitability of Audiology Services

Hearing professionals' services for PwID internationally tend to be based either in hospital settings or community settings. Across the UK, the services also vary by geographical location due to a range of factors including differences in funding streams, overall departmental size, local staff experience and other demands on the service. While there are advantages in services being standardized nationally, local differences in provision can be beneficial if those differences are due to considerations of the needs of the local population. Specialist services for those with a specific syndrome, Down Syndrome for example, may have the advantage of being tailored for the needs of those particular clients,

but at the exclusion of others that could benefit. Services offered for all those for whom standard Audiological care is not appropriate are by design inclusive, but require highly skilled professionals in their operation. Some have separate services for those with intellectual disabilities from birth as opposed to those with cognitive decline relating to for instance dementia, often due to the history of the creation of those services.

Coming to a hospital setting can be unnerving, to the point that an individual may be so anxious that hearing assessment at that visit is not possible. Audiology departments usually include sound proof rooms, for the purpose of hearing testing accurately without interference from background sounds; these are spaces that can be a strange experience for most people. Time can be taken for the client to familiarize themselves with that environment or a further appointment arranged.

3.4. Impact on Other Services

There are other services which have close relationships with audiology. As well as the Ear, Nose and Throat team, a hearing assessment will often have a major impact on the outcomes of Speech and Language Therapy and Psychology. With regards to Psychology, the frequent relationship between hearing loss and poor mental health is well established (Saito et al., 2010; Monzani et al., 2008; De Graaf & Bijl, 2002; Cooper, 1976). This is frequently due to depression arising from isolation (Matthews, 2013). An increasing amount of research suggests that there may be a correlation between hearing loss and cognitive decline, and at the time of writing, a growing body of work is investigating whether therefore the use of hearing aids slows this change (e.g., Ameiva et al., 2015). For individuals with Down Syndrome, dementia often occurs earlier than in the general population (Van Buggenhaut et al., 1999). This, combined with the early onset of presbycusis, can have a multiplicative impact. There are strong arguments for a hearing assessment being a standard part of the dementia test battery, and cognition being considered alongside hearing assessment. As a minimum, links should be in place between services to ensure awareness and ease of referral in both directions.

3.5. Considerations for a Specialist Service Model

Guidelines for Audiological Care for Adults with Learning Disabilities (NHS Scotland, 2009) suggest that a specialist service should be available for this group. Table 1 presents the authors' suggested targets for inclusion in a specialist service.

Table 1. Specialist audiology service considerations

Service Choice	Specialised audiology service for individuals with intellectual disabilities should be offered within a mainstream service and with easy access to that service if preferred by the client.
Staff	- Staff with training and experience in Audiological care for PwID. - Clinic managed by 2 members of audiology team; however, for those who prefer fewer people in the room, the option to be seen by a single member of staff should be available.

Table 1. (Continued)

Staff	• Continuity of care – the same clinicians to see the client throughout their care as far as possible, to reduce anxiety for clients who may find adaptation to change difficult. • A dedicated co-ordinator responsible for evaluating and developing the service and the introduction of initiatives. • A named individual for each referral received who is responsible to ensure their care is delivered.
Location	• Access to the clinic room for orientation before the appointment if requested. • Home visits available if required. • Private or alternative quiet waiting area available if required.
Equipment	• All required equipment available at the time of the appointment to reduce unnecessary additional appointments. • Non-essential equipment cleared away as far as is reasonable to reduce the sense of a “clinical” environment.
Time	• Clinics on different days and times of day with a flexible booking system, allowing the client to be seen at a suitable time. • Longer appointments available, but staff aware of benefits of keeping appointments brief.

4. HEARING ASSESSMENT

There are multiple aims in hearing assessment. Some of the questions the clinician hopes to answer include “What are the quietest sounds this person can hear?,” “Can this person discriminate sound sufficiently to understand speech?” but fundamentally “Does this person have sufficient hearing to lead the life they want to lead?”. Different tests carried out in an Audiology clinic can contribute to answering these questions, ideally in conjunction with the reported experience of sound from the client or carers. The priorities for the assessment should be established early in the clinical encounter. The hearing assessment battery should consist of multiple tests – each test represents different parts of the hearing pathway and there are many instances where 2 people with the same single test result can ultimately have very different hearing capabilities. Only collectively can the assessments inform the Audiologist about the client’s possible experience of sound. In addition to guiding the management process the hearing assessment can also provide an opportunity to demonstrate to both the client and their carers the presence and extent of a hearing loss. This is particularly useful as carers reports are known to overestimate hearing ability (Bent et al., 2015) and a proficient hearing test provides some level of clear evidence.

This section of the chapter aims to present a range of commonly used clinical hearing assessments, their limitations and considerations when being used to assess hearing for PwID. Recommendations for reasonable adjustments are then suggested that could be used to address some of the challenges of these tests.

4.1. Getting to know the Patient's Auditory History

The extent of a hearing loss is often difficult to ascertain by any individual themselves because they may be unaware of the sounds that they have missed. Friends and family members may help to give a view of hearing abilities. This is more so the case for individuals with intellectual disabilities, and family or carers accompanying a client should be asked to report or clarify on all aspects. The Cambridge-Calgary model could be used to frame the appointment (Silverman, Kurtz and Draper, 2013). It is necessary to ensure that possible responses to sounds are not, in fact, responses to accompanying visual gestures or a client's understanding of context. Offering a cup of tea is frequently accompanied with a hand symbol of a cup, and an individual may be very aware that on walking toward a door it will be necessary to get ready without ever hearing "please put on your coat." It may be possible to glean information on hearing from reported reactions to different types of sound. Being more responsive to male voices might suggest that hearing is better at low frequencies. Enjoying some music genres more than others may suggest that there is sufficient hearing to identify the differences. Caution should be used when drawing conclusions on hearing capabilities based entirely on observation – for instance the teenager who turns music up may indeed be a sign of deteriorating hearing, but may also be due to enjoyment commonly gained from loud music. Table 2 presents some observations that may indicate that someone should have a hearing assessment.

Table 2. Behavioral indications of hearing issues

Behaviour directed towards ears	• Puts 1 hand or both over each ear for no reason • Bangs or slaps face • Frequent touching of ears • Unusual head movements • Pulls ear lobes • Cups hand behind ear
Auditory behavior changes	• Developing behaviour that challenges • Unexpected changes in behaviour • Seems confused • A lack of response to specific sounds • Tends to respond more consistently to sound presented on one side • Attention span decreasing
Medical changes	• Frequent catarrh (blocked nose) • Discharge or smell from one or both ears • Dizziness

The communication form that someone has chosen to use may be in part due to an underlying hearing loss. Also, some forms of communication may obscure signs of a progressive hearing loss – for example, with largely visual forms of communication such as Makaton, responses to speech may not change as dramatically as someone who relies on heard speech. While understanding a client's preferred form of communication is a fundamental part of assessing the appropriate management, the reality is that audiology

clinicians with a working knowledge of communication methods such as Makaton, PECS and Objects of Reference are in the minority. Music is often more motivating for people than speech. If someone is involved in music therapy sessions, this may be an opportunity to more clearly identify difficulties in hearing.

Attempts must be made to understand the communication needs of the client, priorities of these needs, and how these fit into their wider needs. The communication needs of people involved in the client's life and their priorities should also be taken into account. There are clients for whom all the information typically gleaned from a hearing assessment will not be achieved. For these clients, consideration has to be given to which aspect of their hearing is most useful to understanding needs, and future rehabilitation and management. The clients and their carers must be involved in this prioritisation. As an example, some individuals are much more interested in music than verbal speech. Should this then be used during the assessment? Can rehabilitation be tailored to maximize music enjoyment over speech discrimination? There are a range of methods used within audiology to record priorities and extent of hearing difficulties being encountered by the patient in situations they are typically in, with recent emphasis on goal setting, such as with individual management plans, and associated outcome measures (BSA, 2012). These should be used before and after any rehabilitation.

4.2. Ear Health

In addition to understanding how well the client hears, the Audiologist is also concerned with ear health. "Otoscopy" involves viewing the outer ear and eardrum using a small light with a magnifier. This allows observation of issues such as infection or earwax in the outer ear. It typically takes under a minute in each ear. This is unobtrusive for many, but individuals who are tactile defensive or dislike other people being in close proximity may find this process uncomfortable.

4.3. Behavioural Assessment

While otoscopy and discussion with the client and those people closest to them is the starting point of a hearing assessment, it is imperative that a hearing assessment goes beyond this. Hearing can be tested in a range of ways depending on aim of the assessment.

4.3.1. Observation

During the initial discussion with the client and anyone they choose to bring to the appointment it is a good opportunity for the Audiologist to observe the client's ability to hear the questions being asked and their interest in conversation. This dialogue may be affected by level of comfort with the situation in addition to their hearing abilities. Observations can also be carried out at home and at day services to evaluate a client's functional hearing, that is how someone uses their hearing.

4.3.2. Audiometry

Pure tone audiometry (PTA) is a standard hearing test to identify the quietest sounds that the individual can hear at a range of tones (frequencies). These levels are then compared to levels expected in those with satisfactory hearing. The client is asked to wear headphones and respond every time they hear a sound which will vary in volume and frequency. The response is often pressing a button, but where there are additional physical disabilities affecting the response, the tester should use a creative approach to enable the patient to respond comfortably and reliably. For an individual with an intellectual disability, there are aspects of this test that may influence its accuracy:

Responses to No Sound

The test depends on an individual's ability to wait. In the general population people occasionally respond when there is no sound presented. This risk tends to be higher for individuals with intellectual disabilities. This may be due to lack of understanding of the need to wait for the sound or the wish to "please" the tester by relating that they have heard a sound even when this may not be the case. There are tactics that the tester can employ to identify when this may occur such as lengthened and more variable gaps between sound presentation, and lateralisation ("ear choice" audiometry (Lloyd & Melrose, 1966)). Lateralisation in this context involves randomly changing the ear that the sound is presented to and asking the client on which side the sound is. For some individuals, this change of task is sufficient to improve the accuracy of the test.

No Responses to Any Sound

While this might be due to the client having severe hearing loss, it is usually known prior to the test whether this is likely from the clinician and client conversation. Not responding to any sound can be due to reduced levels of confidence. Frequent encouragement through the test can be useful. There are instances when the stimulus frequency changes, and the patient does not react to this change immediately. The tester may then misread this lack of response as a lack of hearing to this stimulus.

Starting and Not Finishing

It is necessary to test a range of volumes and frequencies. A client with an intellectual disability may not react to stimulus change immediately. In this instance the tester may misread this lack of response as a lack of hearing. This can be accommodated by re-instructing when changing frequency. Shorter periods of concentration may reduce test duration, so a smaller number of test frequencies may be possible. The tester can extrapolate results to estimate the remaining test frequencies if needed, however this has limitations in accuracy. Also, carers or family members can help to identify the point at which someone has stopped responding due to lack of concentration. The tester may wish to divide the testing into separate sessions to address this issue.

Dislike of Headphones

For some people headphones are unpleasant to wear, particularly those typically used in an Audiology clinic. Presenting the sounds through a speaker (free-field), usually a hand-held device, can address this. This has the advantage of accompanying family or carers being able

to hear the levels of sound at which the individual can hear, and the differences across frequencies. The major disadvantage of this method however is that because the sound is travelling to both ears, it is not possible to be sure which ear is responding.

If there are significant differences in hearing between the 2 ears, it may indicate that further medical investigation is required. Aside from the medical concerns that an asymmetric hearing loss raises, there are other disadvantages in this type of hearing loss. While it is possible to hear well with one ear, if hearing is good in both ears it is easier to “localize,” or identify where a sound is coming from. This has safety implications and can increase the feeling of comfort in a range of situations. Another benefit of hearing well in both ears is that hearing speech in background noise is improved. This is because the brain compares the information from each ear, along with visual cues if we are able to find the speaker and look at their faces.

4.3.3. Visual Reinforcement Audiometry (VRA)

For individuals who do not have the capacity to wait for the presentation of a sound or carry out an agreed action, visual reinforcement audiometry is an option. During this test, a sound is presented through a speaker or headphones and if the client turns towards the source of the sound there is an image of interest to encourage them to continue to turn to sounds so that a range of volumes and frequencies can be tested. Responses to sound in this situation can vary widely and it is imperative that the tester and someone who knows the client well work together to interpret reactions that the client may have in response to sound. There are some who may not make the connection between the sound presentation and the image, however in this case the tester and family member or carer together can observe any responses the client makes to presented sound. Examination of the outcomes of VRA testing at a specialist clinic over the space of a year identified that responses sufficiently reliable to draw conclusions about hearing status were found in a third of clients for whom VRA was used (Dubb & Brennan, 2013).

4.3.4. Speech Discrimination Testing

In addition to identifying the quietest sound that a client can hear, it is useful to identify at what level their hearing can discriminate speech. There are a range of tests available which can consist of a word being presented and the client being asked to either repeat the word or select it from a range of pictures. There are very few tests of speech discrimination that have been verified for use with adults with intellectual disabilities. This should be taken into account when using this type of testing. The extent of the client’s vocabulary should also be taken into account when selecting the most appropriate test. If a presented word is not within the client’s lexicon they may not respond at all or will respond with a similar word that is known to the client and this could be mis-interpreted as a lack of hearing. Another risk of this type of testing is that it is often assumed that speech is the primary sound of interest, however for some individuals this isn’t the case, and lack of interest in the stimulus does not necessarily reflect the inability to hear that stimulus. Additionally, speech tests are sometimes pre-recorded; if someone struggles to recognize words spoken in an unfamiliar accent this can affect the accuracy of the results.

4.4. Electrophysiological Assessment

There are also “objective” measures of hearing assessment. These are ways of testing hearing that do not require an action from the client in response to a presented sound. It is often used when behavioural assessments are not sufficiently repeatable. The majority of these tests can be carried out on an outpatient basis, for which the client should be relatively still and quiet. If this is not possible, some of these types of tests can be offered to take place under general anesthetic; in which case there is benefit to completing on the same occasion as any other procedures the client is to have which require a general anesthetic.

4.4.1. Otoacoustic Emissions (OAEs)

Otoacoustic emissions are often used as a screening tool in babies and younger adults. This test involves placing a small soft tip at the entrance to the ear canal for approximately 2 minutes. A quiet sound travels as far as the cochlea, and the normal hearing ear generates a sound of its own which is recorded by a small microphone. The major advantage of this type of testing is that it is ear specific and very fast. There are disadvantages however: commonly recorded otoacoustic emissions are not frequency specific so someone may have very good hearing at some frequencies but not others and this will not be known. Additionally, this method only tests the auditory system as far as the cochlea and no further, so if there are issues relating to the auditory nerve this will also not be known. The test is only possible if background noise is low – so this test is not appropriate for someone who has perhaps involuntary vocalizations.

4.4.2. Auditory Brainstem Response Audiometry

Auditory Brainstem Response (ABR) testing involves placing electrodes on the head to record the electrical signal travelling up the auditory brainstem portion of the auditory nerve in response to sound presented via headphones. To reduce the response being obscured by electrical activity from other parts of the body the person being tested needs to be relaxed, and can be recorded while the person is asleep. This test is ideal for hearing assessment under general anesthetic. This test can be frequency specific and can take anything from 10 minutes to an hour depending on how much information is needed and how low the background noise is.

4.4.3. Cortical Evoked Response Audiometry

Cortical Evoked Response Audiometry (CERA) also involves placing electrodes on the head to record the electrical signal travelling up the auditory nerve in response to sound presented via headphones; however, due to the nature of the stimulus and recording parameters used, the response recorded originates higher up the auditory pathway. For this reason, this response is dramatically reduced if someone is asleep and therefore not suitable for recording under general anesthetic. This test is also frequency specific and again can take anything from 10 minutes to an hour depending on how much information is needed and how low the background noise is.

4.5. Assessment Recommendations

- Ear canals should be checked regularly and impacted ear wax addressed
- Family members and carers should be involved in the assessment process
- The client should be able to visit the department before their appointment and/or be provided with a story board of the appointment. Images of the staff should also be available to see prior to the appointment.
- A creative approach should be used when attempting behavioural testing.
- The option of testing at the hospital or a home environment should be available. There are major disadvantages to carrying out a hearing test in a domestic environment; they are rarely sufficiently quiet, and not all of the equipment is portable, limiting the testing that can be done, however it may be much more palatable for the client than a hospital setting.
- It may be necessary to use electrophysiology to assess hearing – these techniques should be available and familiar to the tester.
- Research is needed to develop the accuracy and acceptability of Audiological assessment for PwID. Urgent areas include;
 - Optimising test parameters for electrophysiological testing,
 - Verification of speech discrimination tests for PwID.

5. REHABILITATION

The impact of hearing impairment on each person is different. When considering rehabilitation, there are a large number of factors which should be taken into account. What are the forms of communication used by the individual? Will the use of technology, such as a hearing aid, help or hinder that existing form of communication? Is the person with the hearing impairment motivated to improve their hearing? The experience of activity limitations and participation restrictions are equally important as the hearing test in providing the effect and experience of that hearing loss. If an amplification device is being considered, are there barriers to its use, that taken into account with the benefits would result in an overall decrease in quality of life? What reasonable adjustments could be considered to facilitate hearing aid use? Are there equitable alternatives?

5.1. Hearing Aids

Like so many areas of applied science, hearing aid technology is developing at a prodigious rate and satisfaction with hearing aids has increased over recent years. Hearing aids have been shown to improve outcomes for PwIDs as well as the general population (Cupples et al., 2013). Wearing a hearing aid is not equivalent to wearing glasses. Whereas glasses will return most wearer's vision to an experience very similar to that of a non-glasses wearer, the same cannot be said for hearing aids and the hearing impaired listener. When

hearing is impaired, sound is not only quieter, but in most cases also distorted to a certain extent.

The uptake of hearing aids is influenced by a great many factors – some intrinsic to the hearing aids, and some intrinsic to the wearer. Often factors which influence the likelihood of an individual seeking help are also those which impact the likelihood of success with hearing aids when they are issued. Factors external to the hearing aids include self-confidence about ability to manage the hearing aids and support of significant others. Taking the group as a whole, it has been found that the expectations and wishes around hearing aids by individuals with intellectual impairment are similar to those of the general population, including sound quality, cosmetics and comfort (Meuwese-Jongejeugd, 2007).

5.1.1. Setting Hearing Aids

The most common hearing aids are Behind-the-ear (BTE) and In-the-ear (ITE). The BTE consists of an earmould which fits in the outer ear and directs amplified sound into the ear from the main body of the hearing aid which sits behind the ear in the same location as a glasses leg/arm. Earmould selection will depend not only on the Audiological needs of the patient but also the nature of their external ear. A significant proportion of individuals with intellectual disabilities have cranio-facial abnormalities and a higher prevalence of canal stenosis than the general population. Canal stenosis is a narrowing of the ear canal. In addition to often being smaller, the external part of the ear in individuals with Down Syndrome has been found to be softer and shallower than in individuals without Down Syndrome (Miller, 1997). An implication that this has been found to have on hearing aid uptake in this population is the frequency with which the hearing aid will fall from the ear.

The ITE however is a single entity which sits in the outer ear and tends to be more appropriate for mild and moderate losses than severe or profound hearing loss. Additionally, considerations around which to select include ease of insertion, likelihood of loss and risks of ingestion.

The outcomes of the hearing assessment are used to program the hearing aids using “prescription formulae.” These use group data to predict the hearing aid settings that will maximize clarity of speech. The fact that group data is used means that for an individual the optimum settings may be significantly different. Evidence is currently limited regarding the optimum approach to take in hearing aid fitting and management for adults with intellectual disabilities, for example at the time of writing the standard prescription formulae have not been validated in this group. For these reasons, once a hearing aid is set up, the wearer is asked their opinion regarding the quality of sounds, and “aided” speech discrimination tests too. Hearing aid fine tuning can then be carried out accordingly. For individuals with intellectual disabilities, communicative skills may not be sufficient to articulate their opinion on this. Also, questions directed to the wearer should take into account the increased likelihood of acquiescence in individuals with intellectual disabilities.

Programming the hearing aid often requires making Real Ear Measures (REMs). This involves placing a small tube in the ear canal with the hearing aid in place to measure the sound. Placing an identical hearing aid on 2 different ears can sound very different - imagine how different your voice sounds in a cave to how it sounds in your living room! If a client has too much involuntary movement or earwax to make this a safe procedure the hearing aid can be set up in a coupler (a small tube which imitates an ear) using average data called “Real Ear to Coupler Difference (RECD).” However, there are syndromes associated with intellectual

disabilities and hearing loss such as Down Syndrome which present with smaller external ears than expected and the standard RECD may be inaccurate. For these individuals, coupler fittings may be inaccurate. How someone perceives familiar voices will be more crucial than their perception of the Audiologist. Additionally, it can take longer for an individual with an intellectual disability to acclimatise to the voices of people who they are not familiar with. The family member or carer accompanying the client can be involved with establishing whether or not the hearing aid is making a discernable difference to their communication. This could include presentation of different environmental sounds that the client is familiar with presented at different levels.

Multiple programs can be incorporated allowing the user to adjust the hearing aid settings depending on the situations they happen to be in. It is thought that the use of additional hearing aid programs should be removed unless a user has full comprehension of their appropriate use. This may be less of a need as hearing aids are developed with increasingly sophisticated ways of self-adjustment with scene analysis.

5.1.2. Adapting to Hearing Aids

Time is required for an individual to acclimatise to a hearing aid, and for a person with an intellectual disability the introduction of change can be particularly stressful. It is essential that careful consideration and treatment planning is put into place to ensure that the potential benefits of amplification can be gained by those who wish to use them. There may have been an extended period of time between developing a hearing impairment and using hearing aids, as there is a higher incidence of long term undiagnosed hearing loss in this group. The introduction of amplification may be an unsettling experience. If this is not managed appropriately there is a high risk of the patient rejecting amplification entirely. For these reasons in the case of a bilateral hearing loss (in both ears) there is an argument that the first hearing aid fitting should be a unilateral fit (hearing aid for one ear only), and only once it is established that the patient enjoys the use of the hearing aid and gets benefit from it, should a second hearing aid be considered.

Hearing aids are becoming much better in terms of their ability to cope with music. It should be explored at the point of assessment whether the client has an interest in music, so that this can be taken into account in the hearing aid fitting. This could be a stimulus that is used to develop a person's relationship with their hearing aid.

The uptake of hearing aids is known to be poor in individuals with intellectual disabilities if there is insufficient provision of adequate support and follow-up. Review appointments are to assess the outcomes of hearing aid use after it has been worn for a time. In addition to the identification of any logistical issues, discussions should also focus around particular parts of a person's life where they found the hearing aid of benefit or that it caused specific difficulties. "Datalogging" is a feature that allows the Audiologist to discover how frequently the hearing aid has been on. For individuals with multiple programmes and an adjustable volume control, datalogging can also reveal user preferences and indicate whether, for example, the user needs more gain if there is evidence that the volume is repeatedly being turned up. It may take repeated review appointments for a client to fully adapt to hearing aid use.

Some issues relating to rejection of hearing aids may be related to clients and/or their carers not being confident in their use. This can occur in larger institutions where instructions have been issued to a single carer on the date of the hearing aid fitting and that information

has not been effectively passed on to the other members of the patient's care team. This can be addressed by additional training sessions being offered to clients and staff which include reiterating the benefits of a hearing aid for a client with an intellectual disability and hearing loss, insertion and removal of the hearing aid, maintenance including cleaning, battery replacement and trouble shooting.

5.2. Alternative Rehabilitation

For those clients for whom hearing aids are not wanted or appropriate, there are still many benefits of hearing assessment. If the client and their family or carers are aware that there is a hearing issue, a greater amount of support can be offered and hearing tactics can be developed. Also there are a wide range of adaptations and assistive listening devices available, such as connecting fire alarms to the lights, or amplified telephones. The form of communication that someone uses should be considered within the context of their hearing loss.

5.2.1. Hearing Tactics

Hearing tactics refer to strategies that an individual can use to maximize the clarity of the signal being listened to. These tactics make hearing easier for most people, with or without a hearing loss. Training in using these tactics would benefit in particular those who have a hearing loss, but are unable or choose not to wear a hearing aid. For example, Action on Hearing Loss recommended tactics for the listener include:

- Looking at the speaker
- If there is a difference between the ear moving the better ear toward the speaker
- Make the speaker aware of a hearing loss

Tactics for the speaker can include:

- Getting someone's attention before speaking
- Don't cover any part of the face or exaggerate facial movement
- Reducing background noise

There are many more tactics that can assist the listener with a hearing impairment. If a client works with multiple of carers, it would be useful for all of these carers to become familiar with them.

5.2.2. Assistive Listening Devices

In addition to hearing aids, there are a wide range of devices that can be used to complement hearing aid use and others which can be used entirely independently. Devices which can be used with or without hearing aids include loud doorbells, telephones or TV listeners which may use headphones. The form of communication used by an individual with an intellectual disability and whether they are tactile defensive and can tolerate headphones is likely to influence which devices are most appropriate.

If a client uses hearing aids, there are also devices that work with the hearing aid to reduce the impact of background noise. These include frequency modulation (FM) systems. These generally consist of a microphone which is placed as close as possible to the speaker and the signal is transmitted like a radio signal to the hearing aid. FM systems can be either personal FM systems where the speaker may wear the microphone such as in a classroom setting, or FM systems which have a fixed microphone to help in a public setting, such as a bank or theatre. When the user has an intellectual disability care it may be necessary for the individual or anyone supporting them to become familiar with these devices. In some countries these devices are offered through social care services or 3rd sector voluntary organizations. New technology is also becoming available rapidly, including wireless and Bluetooth options for connecting hearing aids to the client's own personal technology such as telephones.

5.3. Rehabilitation Recommendations

- Regular wax monitoring and removal at the GP surgery or Ear Nose and Throat department is recommended for PwID.
- Hearing aid checks relying on questioning should be done with caution in light of possible acquiescence. Measures of hearing aid levels by audiology are recommended instead.
- A range of communication devices should be available alongside hearing aids.
- Hearing tactics should be offered to both PwID and their carers.
- In coming to terms with using and hearing through the hearing aid, both the individual's and their carers' needs should be considered and supported.
- Prior to any demonstration and instructions, patients should be advised on becoming accustomed to the hearing aid, being counselled, encouraged and reassured.
- Both patients and their carers should be provided with verbal and written information as appropriate.
- Other professionals relevant to the individual's care should be considered, such as Hearing Therapy or Speech and Language Therapy specialists.
- Prior to routine monitoring a rehabilitation pathway should continue until the clinician is confident that the auditory needs are realistically met, and that the patient and their carer are having no major practical difficulties with hearing aid use.
- Greater research is needed surrounding Audiological management for individuals with intellectual disabilities. This research should include;
 - comparing the outcomes of different service models,
 - verification of optimising hearing aid fitting targets for PwID,
 - appropriate outcomes for assessing when individualised needs are met.

CONCLUSION

Regrettably, hearing loss is one of the many health issues that is under-identified in individuals with intellectual disabilities. Even if suspected, the effect of hearing loss is often

underestimated or not prioritised. As longevity increases, the prevalence of hearing loss across the population as a whole increases and demands on Audiological care also increase. The need for improved access to appropriate hearing assessment and personalised Audiological care is widely recognised. While there are additional challenges to accessing and utilising audiology services for individuals with intellectual disabilities and hearing loss, this chapter had outlined many steps known to minimise these, and the benefits for most people outweigh the issues. As health and hearing screening programmes continue to expand, the opportunities for accessing audiology services increase. Awareness of sensory needs is increasing.

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Chapter 11

LOOKING WITH EARS, HEARING WITH EYES: VISUAL AND AURAL INTERACTION IN CERVANTES AND SHAKESPEARE

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ABSTRACT

Early modern culture found in the faculties of sight and hearing the highest orders of the senses. They were considered a key to explaining human perceptions, owing to the powerful way in which they can influence and disturb human life. Shakespeare's and Cervantes's treatment of them includes a full acknowledgment of their mental and bodily aspects and functions. As seeing and hearing do not come in a pure state, they mutually interact in the characters and in their responses, which are often contradictory. Since we are visually and aurally minded, it is worth inquiring into how, in Cervantes and Shakespeare, the eye and the ear are used and abused by the characters; how their interaction affects them as hearers and beholders who respond to what is happening by such processes as sympathy or antagonism; and how they make characters react in one way or another, as their actions and emotions depend on what they hear and see.

Keywords: ears, eyes, Shakespeare, Cervantes, perception, emotion, senses, interaction

Early modern culture found in the faculties of sight and hearing the highest orders of the senses. They were considered a key to explaining human perceptions, owing to the powerful way in which they could influence and disturb human life. Shakespeare's and Cervantes's treatment of them includes a positive acknowledgment of their mental and bodily aspects and functions. As seeing and hearing do not come in a pure state, this paper will examine how they mutually interact in the characters and in their responses, which are often contradictory. Since we are visually and aurally minded, it is worth inquiring into how, in Cervantes and

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Shakespeare, the eye and the ear are used and abused by the characters; how their interaction affects them as hearers and beholders who respond to what is happening by such processes as sympathy or antagonism; and how they make characters react in one way or another, since their actions and emotions depend on what they hear and see.

Cervantes, like Shakespeare, shared an interest in the culture of the senses, locating the senses in relation to the body, the mind and society, thereby providing a broader understanding of their centrality in human life. But how can we describe them? How can we differentiate them? Can we really trust them and understand what they signify, as we are often wrong about our own sensations and deceive ourselves about their meaning? In general, the senses are usually considered natural bodily perceptions that have a direct influence on human behaviour. And yet sensory experience varies in time and place, from person to person, from culture to culture, depending on the social and cultural context in which it occurs, so as to make it an important constituent of life.

Though Aristotle first defined the five human senses (436b), definitions and theories about them have varied widely. Augustine maintained that there was a sixth, inner sense, which perceived not only external objects, but also the five senses themselves. He also held that “together, the five bodily organs of sight, sound, smell, taste, and touch express a hierarchy based on how the four physical elements (fire, air, earth, and water) engage the human soul” (in Vance 16). The enumeration of the senses, as well as their anatomical function, relationship to the imagination, and position between spaces inside and outside the body, were big issues within the debate in the late sixteenth and early seventeenth centuries in England and Spain. Helkiah Crooke in *Microcosmographia* (1615) referred to classical sources and contemporary debates, comparing Aristotle, Galen and Vesalius, among others, and presenting his own view in the “Labyrinth concerning the Senses” (716) where he examined the complex nature of senses. He, together with Wright and Reynolds, accepted the model of perception that had its origin in Aristotle’s *De Anima*.

Eyes and ears were held in an exclusive position above the other senses. Although Wright associated vision with the passions and hearing with reason, seeing and hearing were generally viewed as the intellectual senses. They were considered active mediators between the inner self and the outer world. John Bulwer, in his definition of gesturing as a language, conflated seeing with hearing: “for as the tongue speaketh to the ear, so gesture speaketh to the eye” (5). For Sir John Davies sight and hearing were closely tied to thought, as they were the “conduit pipes of knowledge” to “feed the mind.” He groups them above “th’other three” senses (44). However, the Aristotelian model concerning sensation, cognition and the mind, which was so influential in diverse ways in the Middle Ages and the Renaissance, characteristically privileged sight as the noblest sense and most compatible with rational life. Robert Burton in *The Anatomy of Melancholy* (1628) calls sight the most precious sense and the best because it “sees the whole body at once” and because “by it we learn, and discern all things” (157). Shakespeare’s and Cervantes’ treatment of these two senses included a full acknowledgment of the bodily aspects. Their workings also showed the effect of the belief in the humoral composition of the self. Considered in essence processes of the mind, humours were believed to manifest themselves through material symptoms and bodily effects on the senses.

They considered the sight and the ear were complementary senses that made possible the sensorial process. There was, therefore, a close relation between them as Sonnet 23 clearly shows:

O let my books be then the eloquence
 And dumb presagers of my speaking breast,
 Who plead for love and look for recompense
 More than that tongue that more hath more express'd.
 O, learn to read what silent love hath writ:
 To hear with eyes belongs to love's fine wit.
 (9-14)

Shakespeare was aware of the potential of visual and aural power, drawing attention to their connection. In *Venus and Adonis* he sets up a structure of mirroring between the seduction of one character by another and the seduction of the reader by the text. While the attempt to seduce Adonis by Venus is the most obvious aspect of persuasion in the poem, Venus also argues for the disruption of the senses caused by Adonis. There is no resistance to Adonis's voice other than deafness, and his voice penetrates to her heart. But it is not hearing alone that is the problem, and she continues:

Had I no eyes but ears, my ears would love
 That inward beauty and invisible;
 Or were I deaf, thy outward parts would move
 Each part in me that were but sensible:
 Though neither eyes nor ears, to hear nor see,
 Yet should I be in love by touching thee.
 (480-486)

Rather than different senses giving access to different experiences or forms of knowledge, it leads to the same end: love. With it goes the problem of which sense to use in the perception of beauty. While I refer to the relationship between the aural and the visual, it would be wise to note the further step in Venus's speech from eye to ear, from ear to touch. But it is also possible to render this differently; from sight to blindness, from blindness to hearing, from hearing to deafness, and from deafness to touch. One sense activates another, but only at the cost of its own deprivation. Venus's rhetorical display, in which she attempts to argue her way into Adonis's affections, parallels Shakespeare's desire to persuade and seduce the reader. Like the character within the poem, the ear of the reader is open to penetration, to another form of productive hearing. Yet again, such a penetration of the heart comes through the ear, but for the reader this is enacted through the eye.

Sight is the sense par excellence in *Don Quixote*. Countless adventures begin when the knight and his squire see someone or something approaching, and each one sees something different. The power to see, or not to see, and to be seen or not by others, determines Don Quixote's fortunes. The problems of vision and perception become one of the central themes in the two parts. For instance, during the night-long vigil Don Quixote spent guarding his arms, on his very first night out, the moon was "so bright that it competed with the source of its brightness, and every action of the novice knight could be clearly observed by all" (1/3.38). Even darkness turns bright to make his strange appearance visible. But Cervantes does not always set action in clear open landscapes. In *The Trials of Persiles and Sigismunda* (1617) for instance, there are numerous dark and foggy scenes in which it is almost impossible for the characters to see anything. It is as if

Cervantes had decided to place the action in an ideal setting for testing knowledge and theories about optics, refraction, and the anatomy of human sight. He lived at the time “when decisive developments in science, such as the invention of the telescope, were expanding the range of human vision, and when the discipline of ophthalmology was making great advances.” (Echevarría 218).

According to the popular early modern theory of extramission, the eye was seen as the sense for agency and activity. Believed to send out beams to illuminate objects in view, the eye was related to “notions of activity, individualism, aggression, and technical innovation” whereas the ear was related to “passivity” (Folkerth 18). However, this exclusive active attribution of sight was contested by Richard Brathwaite, who suggested that “the Eare is one of the actiuest & laborioust faculties” (12). Besides, “A discreet eare seasons the vnderstanding, marshals the rest of the sences wandring, renewes the minde” (9). Part of the fascination with the ear and hearing stemmed from a clear connection between the ear and the tongue, emphasised by the fact that one could hear oneself speak in a way that one could not see oneself seeing. Stephen Egerton and Robert Wilkinson similarly privileged the ear as the entrance into the deepest reaches of the body. For Wilkinson the ear was the door through which the word of God entered the listener. Thus the ear was given prominence as a direct conduit to the soul.

Though the ear that fascinated early modern anatomists like Crooke, it was also thought as a perfectly sinister vehicle for murder, and one that substantiated fears about aural attention (587). We witness how characters who suffer from sensorial inattention and stands against seemingly more naive alternative views in Shakespeare’s works, such as that expressed in *Othello* by Brabantio: “words are words; I never yet did hear / That the bruis’d heart was pierced through the ear.” (1.3.216-19). The irony of Brabantio’s lack of insight is that Desdemona is indeed won over by Othello’s stories, and the play, which is more frequently read through Othello’s desire for “ocular proof,” is full of references to the ear (1.3.377). Of particular interest here is the movement from hearing to “the eye and the world within speech.” Rupturing any sense of the self-enclosed relay from tongue to ear, Derrida counts self-overhearing as an indication of the continuity of speech and world that refuses to be closed off as an expression of “self.” It is not that there is not a world elsewhere, it is that it refuses to remain safely “over there,” outside the body (in Robson, 1).

In this way, the eye and the ear become problematic senses in Shakespeare, as there is some discord between things seen and heard. Innogen’s first impression of Milford Haven involves a contradiction between what she has heard about and what she sees there. The two senses are also the source of deceit and manipulation, as when Iago suggests that he will “abuse Othello’s ear” (1.3.377) from which Othello’s tragedy arises. Unable to discern the truth between what she has seen and what she hears from Hamlet, Ophelia begins to realize she has been “the more deceived” (3.1.124). She acknowledges her visual and aural abuse from Hamlet:

Like sweet bells jangled out of tune and harsh,
That unmatch’d form and feature of blown youth
Blasted with ecstasy. O, woe is me,
T’have seen what I have seen, see what I see!
(3.1.156-59)

Besides, the eye and the ear can cause confusion, as there is much discrepancy between what is seen and heard and what really happens. This confusion between sight and sound is clearly expressed by Hero's answer "Nothing certainer" to Claudio's question "Another Hero?" (5.4.62), posing a big question mark over sensory perception. The same reserve and questioning of the two senses appear in *Hamlet* where two radically opposed epistemologies are at crossroads. "On the one hand, thinking happens only through the body and its properly functioning perceptions. On the other hand, Shakespeare's era witnessed an increasingly serious skepticism over their viability as mechanisms to secure knowledge" (Marchitello 139). The Prince is not the only one who sees his father's ghost in the opening scene of the play; but later, in the bedroom scene with his mother, Hamlet is the only one who can see it (3.4.105). For him, the ghost's appearance is something real, while Gertrude only sees Hamlet addressing an empty space. What Shakespeare might be querying here is whether something can ever be considered real or true if only one person can see it; in other words, he questions the limits of vision of truth that requires social confirmation before it can be accepted.

In many ways, *Don Quixote* is a novel about how Don Quixote perceives the world and about how other characters perceive Don Quixote. His tendency to transform everyday people and objects into more dramatic, epic, and fantastic versions of themselves forces those around him to choose between adapting to his imaginary world or opposing it. Some, such as the barber and the priest, initially try to coax Don Quixote back into a more conventional view of the world and away from his unconventional life as a knight-errant. To get Don Quixote to communicate, however, they must play along with his world, pretending to believe in his wild fantasies. By the end of the novel, these characters achieve a more harmonious relationship with Don Quixote's fantasy world, recognizing its value even if they do not believe it is literally true.

Those who oppose Don Quixote—namely, Sampson Carrasco and the Duke and Duchess—find their lives disrupted by Don Quixote's perceptions of the world. Sampson temporarily becomes a knight to seek vengeance on Don Quixote, sacrificing his own perceptions of the world because he is obsessed with altering Don Quixote's world. The Duke and Duchess find that the people and events around them actually match Don Quixote's vision much more closely than they expected, as adventures such as Sancho's governorship and the adventure of Doña Rodriguez fit well into Don Quixote's world and not so well into their own.

Perception and deception are major topics in Cervantes's interludes, in which the capacity to deceive, to be deceived and to deceive oneself becomes a central concern. The eight interludes are variations on the binaries of illusion and reality. Language is used to deceive as in *The Sham Biscayan*, whose trickster-protagonist employs a stylized Basque dialect, in *The Cave of Salamanca* through the character of the wife who must convince her husband of her love, although she has none, and in *The Jealous Old Man* in which the discovery of truth fools the jealous old man. In *The Miracle Show* the power of the word is not only capable of manipulating the characters on the stage, but also of deceiving the public through aural and visual confusion. But if Cervantes sometimes seems to approve deceit, it is only to show how human foolishness can justify it.

But sensorial abuse can have powerful, even dangerous, effects on the human body. Romeo, like Demetrius in *A Midsummer Night's Dream*, acknowledges the deceptive as well as fleeting nature of visual and aural perceptions, which are as insubstantial as dreams and "smoke" that vanishes in the air. *Romeo and Juliet*, there are a number of characters that are

prone to an excess of emotion. Romeo in particular seems to have an addiction to emotion, as his speeches reveal. When Romeo describes his love for Rosaline, for example, he says “Love is a smoke made with the fume of sighs, / Being purged, a fire sparkling in lovers’ eyes, / Being vexed, a sea nourished with lovers’ tears. / What is it else? A madness most discreet” (1.1.187–191). But love, with its binding, twisting labyrinth of emotions, often has diverse effects on those caught in its grasp. It is an overwhelming, overpowering emotion beyond reason, producing “most discreet” madness as in the case of Don Quixote:

And in the porches of my ears [he] did pour
 The leperous distilment whose effect
 Holds such an enmity with the blood of man
 That swift as quicksilver it courses through
 The natural gates and alleys of the body
 And with a sudden vigour it doth possess
 And curd like eager droppings into milk
 The thin and wholesome blood.

(1.5.63-70).

However, not only the text and the reader, but also the writer may be seen as an indispensable source of sensorial power/influence. He cannot remain indifferent to what happens, particularly in emotional contexts. The writer is somehow involved in what he writes about. He plays a central role in the creation of fictional networks. Accordingly, having some knowledge of the authorial affective engagement would enable us to know more about what is going on in the text, as well as about the characters. Otherwise, we would be missing relevant information in the exploration of the senses. The problem lies in the fact that we have no direct access to this knowledge; such is the case of Shakespeare’s Sonnets which are deeply personal, disclosing the author’s most private sentiments.

Besides visual and aural activity becomes more complex when the same character encompasses and integrates diverse experiences. Radical changes in the same character abound in Hamlet and Don Quixote from the beginning. How can we explain those extreme behaviours? Why does Don Quixote see a giant in a windmill; or does Macbeth have the vision of the dagger? At this point we should consider that every action, however trivial, leaves a mark on the characters and becomes a causal link for the rest of their lives. It is through apperception that “...new experience is assimilated to and transformed by the residuum of past experience of an individual to form a new whole” (Runes). They perceive new experience in relation to past experience. It means that what we perceive through the eyes and the ears is more than mere sensations, as Don Quixote and Hamlet show. Their visual and aural perceptions cannot be separated from their basic experiences and commitments. When Don Quixote says in relation to Dulcinea, “I imagine that everything I say is precisely as I say it is, and I depict her in my imagination as I wish her to be, both in beauty and in rank” (1/25.216), he describes a process through which he can define his own reality. Two different meanings can be rendered from the physical and psychological connotations of the verb “to see” at this point: to accept as fact everything the eyes see, or to believe everything the mind thinks. However, Don Quixote often sees with his eyes manifestations he creates in his mind. In the episode of “Mambrino’s helmet” he says to Sancho “Tell me! Do you not see that knight coming towards us, upon a dapple-grey steed,

wearing a helmet of gold?” to which Sancho replies “All I can make out...is a bloke on a donkey, brown like mine, with something shiny on his head.” (1/21.166). Don Quixote believes everything he hears or sees is exactly as he interprets it in his imagination. In many ways, Don Quixote is about how Don Quixote sees the world and about how other characters see Don Quixote. His tendency to transform everyday people and objects into more dramatic, epic, and fantastic versions of themselves forces those around him to choose between adapting to his imaginary world or opposing it.

The ear and the eye also appear as subjects rather than objects. They actively do things. They are not merely specialized anatomical faculties for receiving stimuli. In *Coriolanus* appearances and hearing play a central role, as the characters’ actions are motivated by what is seen and heard rather than what is thought. Shouting and violence, noise and visual manipulation, make it hard to live in the city of Rome, as we learn right at the opening of the play when the common people are rioting against the patricians. They make it clear that “Caius Martius is chief enemy to the people” (1.1.7). In return, he also despises the mob, though he is dependent upon them. His antisocial attitude reflects his fragmentary and dichotomous perceptions. Coriolanus’s tragedy lies in his inability to react against what he hears and sees. Moreover, family ties make Coriolanus’s perceptions fragile and contradictory, such as when his mother pleads with him to give up his real feelings in order to get the consulship nomination. He underestimates the power of the senses that finally produces a permanent maladjustment, as he is incapable of adapting to the critical situation of Rome burning in popular rebellion. But sensations are transitory, shifting and provisional. Coriolanus will no longer be a Roman hero but a “traitorous innovator” among the Volscians.

In Shakespeare and Cervantes, characters use the information gathered through the eyes and the ears to achieve particular goals, as well as to change others’ perceptions and situations in form and degree for a particular reason, producing an immediate reaction and creating conflicts that can cause the transformation of other characters through sensorial processes. Besides, the senses are conveyed through interpersonal dynamics that also depend on the particular temperament and reaction of the characters, giving them a new insight into those events and providing them with a different experience. In the case of “The Tale of Inappropriate Curiosity” (1.33), while the priest is reading the story, the characters/listeners are observing the performance. At the beginning Anselmo composes a drama in which his friend, Lotario, plays the role of seducer so that he can see the reaction of his wife, Camila. But when the fiction becomes reality, and Lotario actually does become Camila’s lover, they plot a counter-drama, in which Camila will be the protagonist, forcing Anselmo to assume the role of spectator. Ultimately, Anselmo becomes the victim of the plot he has devised.

Observing and perceiving, therefore, are regarded as a dynamic and immersive process of exchange between the viewer and the viewed, between the hearer and the sound, and between the performer and the beholder. In this way, characters create a network of sensorial interaction with other characters, who are somehow forced to respond. Sophie Ratcliffe has explored the relationship between sympathy, knowledge and perception underlining the function of sympathy as a vehicle for connecting characters. It implies an effective involvement of the characters as hearers, viewers and beholders. They generate reactions of different sorts in other characters that affect their responses. While waiting for Sancho to return, the priest and the barber encounter Cardenio, who tells them his story:

Suspecting Don Fernando's treachery as little as I did, she told me to try to come back soon, because she believed that the accomplishment of our wishes would be delayed by no longer than our fathers' conversation. I don't know why, but when she finished saying this, her eyes filled with tears and a knot seemed to form in her throat, stopping her from speaking any more of the very many words that she appeared to want to say to me. I was astonished at this strange faltering, because it had never happened before and, whenever good fortune and my diligence had allowed us to talk, we'd done so with great joy without any tears, sighs, jealousy, suspicion or fear. I would dwell on my good fortune, because heaven had given her to me as my lady; I would extol her beauty, marvel at her merit and her understanding.

(1/27.235)

Cardenio's account is the only access to Luscinda's reaction. We then get the full story from Cardenio because Don Quixote is not present to interrupt the storytelling. Cardenio, like Don Quixote, appears as a grief-stricken character who stumbles through a life of unrequited love.

Witnessing the pain of others through the spectacle of suffering is another form of visual and aural interaction. Nowhere in *King Lear* do the traumatic episodes produce bewilderment more clearly in the viewers than in act 4.6. when we see the blind Gloucester being led to Dover by the disguised Edgar:

Gloucester. When shall I come to th' top of that same hill?

Edgar. You climb up it now: Look how we labour.

Gloucester. Methinks the ground is even.

Edgar. Horrible steep

Hark, do you hear the sea?

Gloucester. No, truly,

Edgar. Why, then, your other senses grow imperfect

By your eyes anguish.

Gloucester. So it' may be, indeed:

Methinks thy voice is altered and thou speak'st

In better phrase and matter than thou didst.

Edgar. You' re much deceived: in nothing am I changed

But my garments.

Gloucester. Methinks you're better spoken.

(4.5.1-14)

Thus the play makes us acutely aware of the horror of gratuitous violence, and offers no consolatory prospect that humans might act differently. It is indeed an inverted and violent world. As "senses grow imperfect," pain, violence and cruelty develop in Shakespeare's plays as a sensational element, where characters not only know how to be violent but also assume their right to use violence. Edgar is trying hard to lead Gloucester away from reality, placing him in a world of his own perception. Edgar is cruel only to be kind, frustrating Gloucester's suicide. Don Quixote's violence works in a different manner. It is cruel not to be kind but to be comic.

The characters are also an indispensable source of sensorial power/influence. They cannot remain indifferent to what happens, and are somehow involved in what they see and hear. They play a central role in the creation of fictional networks, as they have the sense of

being there and of participating in what is going on. Thus Shakespeare and Cervantes also bring us up close to the characters to see them, hear them, and witness the subtlest changes. Furthermore, our perceptions are channelled to us by way of the consciousness of characters who themselves are witnesses of the action. This suggests that characters assume the tasks that we would otherwise assume more directly, and our perceptions depend on their hearing, seeing, and feeling. *Don Quixote* —from about Chapter 15 until nearly the end of Part I— continually directs our attention to those who respond emotionally to something or someone else. Our only access to events is often by way of witnesses' responses:

A little before dawn the ladies heard a voice which was so fine and tuneful that they all had to listen, particularly Dorotea, who was already awake and by whose side Doña Clara de Viedma, the judge's daughter, was fast asleep. None of them could imagine who it was singing so well, and unaccompanied. Sometimes the voice seemed to be coming from the courtyard, at other times from the stables; and as they lay there listening in bewilderment Cardenio came to their door and said:
—If any of you are awake, do listen and you'll hear a young footman singing. It's the most gorgeous sound: enchanting chanting, one might say.
—We're already trying to listen, sir, Dorotea replied.
So Cardenio crept away, and Dorotea, listening as hard as she could, heard that what was being sung was the following...

(1/43.401)

Our only connection to that voice is by way of those characters who hear it and react to it in awe, thus giving form and colour to our own expectations. Much the same interaction occurs in other cases, as when the Pérez de Viedma brothers, the captive and the judge or *oidor* meet up in 1/42. A very excited Ruy Pérez confirms that the newcomer to the inn is his brother, but he is assailed by doubts about whether this brother will receive him well. Hence the priest's intervention to clarify it, and while the priest puts the *oidor* to the test, we feel the intensity of the emotions of the captive, who is watching and listening to every sound, while the attentive *oidor* is overwhelmed by what he hears. He "was all ears – never had he heard any case as attentively as he did this one" (1/42.398).

In *Twelfth Night* the reunion of the twins is the inevitable climax of the play; before this moment, Sebastian has had no idea that Viola could still be alive, so he manifests his disbelief at hearing and seeing her again, dressed to look like him:

Ant. How have you made division of yourself?

An apple cleft in two, is not more twin

Than these two creatures. Which is Sebastian?

Oli. Most wonderful!

Seb. Do I stand there? I never had a brother;

Nor can there be that deity in my nature,

Of here and everywhere. I had a sister,

Whom the blind waves and surges have devoured.

Of charity, what kin are you to me?

What countryman? what name? what parentage?

Vio. Of Messaline: Sebastian was my father;
 Such a Sebastian was my brother too,
 So went he suited to his watery tomb.
 If spirits can assume both form and suit
 You come to fright us.

Seb. A spirit I am indeed,
 But am in that dimension grossly clad
 Which from the womb I did participate.
 Were you a woman, as the rest goes even,
 I should my tears let fall upon your cheek,
 And say 'Thrice-welcome, drownèd Viola!'

(5.1.207-227)

Viola is calmer, since her encounter with Antonio led her to think that Sebastian was still alive and well; yet, there is great emotion on both sides at this lucky reunion. But Sebastian and Viola need to see and hear each other to believe it. Visual and aural perception is the ultimate reason for their mutual recognition. At last, the theme of mistaken or hidden identity is resolved, with everyone having been revealed as their true selves.

Cervantes and Shakespeare show the variety and complexity of sight and hearing, with an emphasis on its bodily material aspects, so as to involve the reader/spectator in the event. What matters is not only what happens in the text, but also how it is visually and aurally perceived and how it affects other characters. It is not only the act of hearing or seeing the event that is relevant, but also the representation of the emotional and sensorial framework created by the characters. In this way, they anticipate modern ways of experiencing and representing perception and the senses. They show us how we can discover a world of new experiences and sensations of which "The eye of man hath not heard, the ear of man hath not seen..." (MND 4.1.201-202).

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Chapter 12

UNIVERSAL NEWBORN HEARING SCREENING IN THE UNITED STATES

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ABSTRACT

Hearing impairment or loss can be defined by the partial or total inability to hear sounds experienced in the environment, represent a wide spectrum of disease due to congenital or acquired causes and seen with various developmental disorders requiring early intervention services for optimal health outcomes. Early detection to decrease morbidity and prevent life-long disability was the principle of newborn screening adapted to Universal Newborn Hearing Screening. We explore how Universal Newborn Screening evolved, from history to epidemiology, from policy to shaping of a public health program and from cost benefits of current universal screening to possible next steps in decreasing morbidity and preventing lifelong disability nationally and internationally.

Keywords: newborn hearing screening, hearing loss, public health

INTRODUCTION

Hearing impairment or loss is the partial or total inability to hear sounds experienced in the environment. According to the World Health Organization (WHO), there are approximately 360 million people worldwide with hearing impairment (1). Hearing

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impairment is a diagnosis encompassing a wide spectrum of presentations and disease processes, a vital impact on human development, a major public health concern, a battleground for cultural identity and the conception of health, and a research field rich with ongoing questions. Hearing loss can be further differentiated into conductive and sensorineural hearing loss (SNHL) and can be unilateral or bilateral or differentiated by different risk factors (2). Auditory anatomical and physiological shaping begins early in embryologic development and is refined throughout early childhood, which has important implications for possible congenital and acquired hearing impairment resulting from toxic exposures to underlying genetic defects. The epidemiology of newborn hearing loss along with the ease of available technology was instrumental in the development of “Universal newborn hearing screening” (UNHS) programs in the US and worldwide. Discussion about UNHS in the United States is incomplete without understanding the history and evolution as a public health program with active participation of all stake holders—parents, specialists, professional societies and the government.

EPIDEMIOLOGY

Best evidence on national prevalence of newborn hearing loss is noted in the MMWR 2010 report (3) with CDC (Center for Disease Control and Prevention analysis of EHDI (Early hearing detection and intervention) surveillance data in United States from 1999-2007; geared to determine the status of efforts to identify newborns and infants with hearing loss. Though, data until 2005 was passively reported to CDC, 2005-2007 CDC-EHDI active data collection did not demonstrate a huge difference between prevalence of newborn hearing loss – 1.1 versus 1.2 per 1,000 screened; even though the percentage of infants screened increased from 46.5% in 1999 to 97% in 2007 and the number of States reporting increased from nine States and territories to 44 States and territories. In January 2000, Statement of the American College of Medical Genetics on Universal Newborn Hearing Screening noted that hearing loss is present at birth in 1-2 per 1,000 infants (4). The CDC-EHDI prevalence data in the US is similar to public and private institution reports in different European countries/regions, but there seems to be reports of higher prevalence of newborn hearing loss reported from developing countries as noted in Table 1.

Table 1. Prevalence of hearing loss

Country	Prevalence	Author	Published year	Pubmed reference
United Kingdom	1.8 per 1000	Watkin et al. (5)	2012	22686437
Switzerland	1.2 per 1000	Metzger-Müller et al. (6)	2013	24338080
Ireland	1.3 per 1,000	O’connor et al. (7)	2013	23456183
Israel	1.3 per 1,000	Gilbey et al. (8)	2013	23122541
Belgium	1.5 per 1000	Van Kerschaver et al. (9)	2013	22452806
Turkey	2.2 per 1000	Tasci et al. (10)	2010	20015280
Brazil	0.96 per 1000	Bevilacqua et al. (11)	2010	20303604
Brazil	2 per 1000	Oliviera et al. (12)	2013	24142311
UAE	2.6 per 1000	Ur Rehman et al. (13)	2012	23301401
India	8 per 1000	Rai et al. (14)	2013	23642585

THE HISTORY OF UNIVERSAL NEWBORN HEARING SCREENS (UNHS) IN THE UNITED STATES

The history of Newborn Screening for any disorder is incomplete without mentioning Dr. Robert Guthrie's (1916-1995) work establishing PKU (phenylketon-uria) screening in 1960s as a public health program initiative in the State of Massachusetts. Though, around the same time as initial PKU screening, a varied range of efforts by different disciplines towards early detection, diagnosis and intervention for hearing loss were in the works Downs et al. (15, 16) and, initial hospital based screening for hearing loss took place as early as 1970s. By the late 1980s, Dr. C. Everett Koop (1916-2013), then US Surgeon General, pioneered that detection of hearing loss to be included in the Healthy People 2000 goals for the nation (17).

In 1988, the Maternal and Child Health Bureau (MCHB), a division of the US Health Resources and Services Administration (HRSA), funded pilot projects in Rhode Island, Utah, and Hawaii to test the feasibility of a universal statewide screening program to screen newborn infants for hearing loss before hospital discharge (18). Wide spread practice of hospital based screening did not occur until after the 1993 NIH Consensus Development Conference on Early Identification of Hearing Impairment in Infants and Young Children that recommended that all newborn infants be screened for hearing shortly after birth (19).

O March 18, 1999, Congressman James Walsh (R, NY) introduced the Newborn Infant and Hearing Screening and Intervention Act of 1999 (20). In May, 1999, Senator Olympia Snowe (R, ME) introduced the companion bill in the Senate. At the end of the legislative session, federal appropriations committees in both the House and Senate earmarked new funding for newborn hearing screening. The language was included in the Omnibus Appropriations bill President Clinton signed in November, 1999. This landmark federal legislation 'Newborn and Infant Hearing Screening Intervention Act of 1999' enacted by the federal government provided funding to states from the Health Resources and Services Administration and the Centers for Disease Control and Prevention to support the infrastructure required for planning, development, implementation, and refinement of early hearing detection and intervention (EHDI) programs and for EHDI tracking and data management systems. Universal Newborn Hearing Screening as an essential component of early detection and intervention for infants with hearing loss was adopted after support from multiple professional societies, advocacy groups, and government agencies participating in the Joint Committee on Infant Hearing (JCIH) (21, 22).

In 2007, the Joint Committee on Infant Hearing (JCIH) endorsed early detection of and intervention for infants with hearing loss through integrated, interdisciplinary community, state, and federal systems of universal newborn hearing screening, evaluation, and family-centered intervention (23). The goal of EHDI was determined to maximize linguistic and communicative competence and literacy development for children who are deaf or hard of hearing. The updated 2007 JCIH position statement delineated specifics addressing:

- Definition of targeted hearing loss;
- Hearing-screening and -rescreening protocols - separate protocols recommended for NICU and well-infant nurseries;
- Diagnostic audiology evaluation by Audi-ologists with skills and expertise in evaluating newborn and young infants and including ABR testing;

- Medical evaluation including genetics and otolaryngology consultation for every confirmed hearing loss;
- Early intervention service establishment;
- Surveillance and screening in the medical home;
- Communication between the birth hospital, State and parents;
- Information infrastructure for data management and outcome tracking.

The national resource for EHDI at the National Center for Hearing Assessment and Management (NCHAM) provides timeline, summary and details of each State specific mandates and enacted Newborn Hearing Screen legislation (24).

After 10 years of being introduced as a legislation, in December 2010, the United States Senate and the House of Representatives each voted to approve the Early Hearing Detection and Intervention Act of 2010 (HR. 1246, S. 3199). President Obama signed the legislation into law on December 22nd 2010 (25, 26).

The Early Hearing Detection and Intervention Act of 2010 amends the Public Health Service Act to: 1) expand the newborn and infant hearing loss program to include diagnostic services among the services provided and 2) require the Secretary of Health and Human Services (HHS), acting through the Administrator of the Health Resources and Services Administration, to assist in the recruitment, retention, education, and training of qualified personnel and health care providers to implement the program.

It revised program purposes to include: 1) developing and monitoring the efficacy of statewide programs and systems for hearing screening of newborns and infants, prompt evaluation and diagnosis of children referred from screening programs, and appropriate education, audiological, and medical interventions for children identified with hearing loss; 2) developing efficient models to ensure that newborns and infants who are identified with a hearing loss through screening receive follow-up by a qualified healthcare provider and 3) ensuring an adequate supply of qualified personnel to meet the screening, evaluation, and early intervention needs of children.

It amended the definition of “early intervention” to require that families be given the opportunity to obtain the full range of appropriate early intervention services, educational and program placements, and other options for their child from highly qualified providers.

It requires the Secretary to establish a postdoctoral fellowship program to foster research and development in the area of early hearing detection and intervention.

The 2013 supplement to the recommendations in the year 2007 position statement of the Joint Committee on Infant Hearing (JCIH) provides comprehensive best practices guidelines for early hearing detection and intervention (EHDI) programs on establishing strong early intervention (EI) systems with appropriate expertise to meet the needs of children who are deaf or hard of hearing (D/HH) (27).

COST BENEFIT

The varying disease burden in different parts of the world as noted under ‘Epidemiology of newborn hearing loss’, along with more recent data suggesting need of targeted surveillance in at-risk children who pass the hearing screen (5, 28) or school entry hearing

screening as in the United Kingdom (29) requires us to take into consideration of cost benefit of universal hearing screen and its implementation as a public health program across the world. We know that implementation of any public health program includes a cost- benefit analysis of a proposed project – a process by which the costs of a program to proposed benefits to the individual and society is taken into consideration. Often such calculations are based on available literature as evidence or conducted prospectively taking outcome measures into consideration.

There is a paucity of comprehensive long term data in form of randomized control trials, or observational parallel cohorts or epidemiological evidence that takes into consideration at all probable variables and outcomes. In general, cost of universal newborn hearing screening (UNHS) include capital (cost of equipment) and operating expenses (costs for disposables and personnel), as well expenses for follow-up (diagnostic testing costs) and early intervention programs and services. Taking into consideration various model assumptions, it was shown that even though initially, the costs of UNHS exceed its benefits; but there are short term and long term reaching a maximum annual benefit of seven billion dollars 75 years after initiation of the program, which also results in the societal benefit for all years thereafter (30).

Short term cost benefits analysis projects the benefit of improved language reduced the lifetime costs associated with deafness by approximately \$430 000 per deaf individual (31). Long-term benefits, both individual and societal are yet to be predetermined conclusively and understandably difficult to estimate with accuracy. With varying prevalence of newborn hearing loss in different parts of the world, the cost-effectiveness of universal newborn hearing screening (UNHS) in United Kingdom was compared to selective screening of newborns with risk factors in India (32) and demonstrated that the cost-effectiveness of a screening intervention was largely dependent upon two key factors: the cost (per patient) of the intervention drives the model substantially, with higher costs leading to higher cost-effectiveness ratios and the baseline prevalence (risk) of hearing impairment. Though, the economic limitations of developing countries or regions may warrant implementation of ‘at-risk’ or targeted newborn hearing loss screening more feasible than UNHS (33, 34). There are also suggested values in adding bloodspot-based genetic testing of common mutations as second tier testing for bedside newborn hearing screening (35).

CONCLUSION

Universal newborn hearing screening helps with early diagnosis and intervention of hearing impairment - a complex and multi-faceted public health concern that can have long-term impacts on health, education, and quality of life outcomes in a child and a future generation. There may be a paradigm shift requiring a second phase to UNHS with pre-school based screening to improve long term educational and quality of life outcomes. Lifetime costs associated with hearing loss per child/disabled adult far outweighs costs of UNHS or early childhood screening.

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Chapter 13

HEARING LOSS IN NEONATAL INTENSIVE CARE UNITS (NICUS): FOLLOW-UP SURVEILLANCE

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ABSTRACT

Infants admitted to the neonatal intensive care unit (NICU), who represent the 4-8% of all births, present problems such as prematurity, low Apgar scores, infections, hyperbilirubinemia and hearing impairment. In particular significant hearing loss is the most common disorder at birth, occurring in 1 to 2 newborns per 1000 in the general population and 24% to 46% of newborns who are admitted to a NICU. This leads more difficulty to develop verbal skills (learning vocabulary, grammar, word order and idiomatic expressions), language, learning and speech. Hearing impairment influences also cognitive and affective development of infants making consequences in their interpersonal relationships. Joint Committee on Infants Hearing (JCIH) identified many risk factors in NICU infants like as prolonged mechanical ventilation, asphyxia, low birth weight and ototoxic medication and therefore the first step for early diagnosis of hearing loss is identify these factors. Second step is to plan a correct screening strategy. Screening procedures to detect hearing impairment may be divided into two categories: behavioral and electrophysiological. Behavioral techniques produce a high number of false-negative results due to the relative subjectivity of the assessment and difficulty in detecting mild or unilateral hearing loss. Electrophysiological procedures have greater

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sensitivity and specificity and include measuring the following: auditory brainstem responses (ABR), automated auditory brainstem responses (AABR), and evoked otoacoustic emissions (EOAE). In this chapter will analyze the prevalence of the risk factors in NICU infants most often associated with hearing loss and the screening methods to arrive as soon as possible an early diagnosis.

INTRODUCTION

The prevalence of hearing impairment among infants varies between 0.5 and 3.0 cases per thousand, but in children hospitalized in neonatal intensive care unit (NICU) the prevalence is 10-20 times greater [1, 2, 3]. The international guides claim that an important factor for the risk of hearing loss is the hospitalization in NICU for more than five days, in fact, in these cases it is recommended the audiological screening with A-TEOAE and A-ABR followed by a close follow-up.

The hospitalization in NICU contains a number of risk factors for the development of hearing loss, such as prematurity, low birth weight, the use of ototoxic drugs, hypoxic ischemic insult, hyperbilirubinemia requiring exanguino-transfusion. In most cases, the hearing loss is associated to the coexistence of more than one of the above conditions, as these are often related to one another [4].

Following, an analysis of the most important risk factors in the newborn NICU will be performed with particular attention to follow-up surveillance.

CYTOMEGALOVIRUS

Congenital CMV infection is transmitted to the fetus through the placenta with a transmission rate of about 32% in the case of primary maternal infection and about 1.4% in the case of reactivation or reinfection CMV seropositive. CMV infections can therefore represent the hidden etiology of many cases considered of unknown origin and is probably the most frequent cause of non-genetic hearing loss, as well as the most frequent cause of congenital defect and disability in children [5].

CMV infection is one of the most frequent causes of neonatal SNHL, in fact 25% of hearing losses arising before the fourth year [6, 7]; it can be associated with microcephaly, visual impairments, motor and cognitive disabilities, cerebral palsy and seizures (symptomatic form). 33-50% of cases of SNHL related to congenital CMV infection are delayed-onset and occur early in life, usually after 11 months in asymptomatic respect to symptomatic. The hearing deficiency occurs frequently progressive and fluctuating, involving some frequency, unilateral or bilateral [8]. Foulon et al. showed, in 68 children with congenital cytomegalic infection and subjected to three audiological evaluations in the first 18 months of life, a tardive SNHL in 4.3% cases, unstable in 29,8% and fluctuating in 16.2%. In the cases of hearing impairment, it was observed a worsening of the hearing threshold in 27.3% of patients and an improvement in 40.9% [9]. Given the heterogeneity of the clinical picture and the risk of late-onset or progression of hearing loss, it is recommended careful monitoring by means of audiological evaluations performed at 6 month intervals until the fifth year of life and a closer follow-up every three months until the child begins to speak.

BACTERIAL MENINGITIS

Among the postnatal bacterial meningitis, 5-35% of patients can present a damage of the cochlear neuroepithelium in with a profound bilateral sensorineural hearing loss. Kutz et al. analyzing data from a cohort of 134 children (mean age of 3.4 years) and between these, 30.6% of bacterial meningitis were identified. Some of these patients with a sensorineural hearing loss, above all in cases with unilateral involvement and mild grade, showed to a few months from infection the tendency to regression [10]. Adachi et al. and Ballacchino et al. carried out a diagnosis of SNHL in 24% of the bacterial meningitis, showing a profound degree of hearing loss in about half of the subjects and a greater risk of audiology in case of pneumococcal etiology [11, 12].

HEAD INJURY

Head injury, associated or not with temporal bone fracture, is in 23-64% of cases, a potential cause of transmission, sensorineural or mixed hearing loss. Dunklebarger et al. found, in 71 children with head trauma history associated with temporal bone fracture, the presence of sensorineural hearing loss and transmission respectively in 20% and 24% of cases. Evidence of damage to the otic capsule was found a positive predictor of SNHL ($p = 0.025$) [13, 14]. Bowman et al. proposed an algorithm to identify children at greater risk of hearing impairment after head injury in case of radiological evidence of temporal bone fracture, patients under the age of three years, subject with Glasgow Coma Scale (GCS) < 13 with or without loss of consciousness. For those “low-risk” the authors suggested performing audiometric tests only in cases of clinical evidence of hearing loss. However, this algorithm has some limitations because it doesn't identify the forms of hearing impairment caused by mild head trauma or those forms no identifiable by recording OAEs or not discoverable subjectively by the infant [15].

OTOTOXIC DRUGS

In the neonatal period ototoxic drugs, above all some antibiotics and diuretics, are a risk factor for SNHL with early and delayed onset. In fact, an audiological follow-up and hearing screening must be made by the 24th-30th month of life to the children that these drugs were administered. Despite these guidelines, the results of some recently published studies have highlighted controversial aspects about the actual risk of hearing loss following administration of aminoglycosides and diuretics. Vella-Brincat et al. analyzing the results of the 2347 OAEs recorded in newborns admitted to NICU, they showed a higher risk of absence of otoacoustic emission in patients treated with vancomycin ($p = 0.003$), in contrast to individuals observed in exposed to gentamicin alone where this risk was even reduced [16, 17]. Similar findings were reported by de Hoog and Kraft, who have not observed an increased risk of hearing loss in newborns to undergo therapy with tobramycin, respectively, and diuretics. A special mention deserve those individuals submitted to therapy with aminoglycosides because carrier of mitochondrial mutations m.1555A $> G$. About ototoxic

chemotherapy drugs (cisplatin and alkylating agent) used in pediatric oncology, it was associated with progressive symmetrical bilateral SNHL initially limited to high frequencies. The hearing deficiency can occur even several months after completion of chemotherapy cycle, more frequently in subjects during treatment do not show any impairment of hearing thresholds. This entails the indication to submit such patients to a hearing assessment before chemotherapy and to a regular follow-up [18, 19]. Al-Khatib et al., in a retrospective work performed on 31 children with treated with cisplatin, revealed a variable degree of hearing loss from mild to severe in 42% of cases; in particular, the long-term follow-up audiological (1.5 to 6.6 years) of the 21 individuals studied, showed a worsening of audiometric threshold in 33% of cases (7/21) with the need, in 5 subjects, of prosthesis [20, 21].

FOLLOW-UP SURVEILLANCE

To date the application of audiological monitoring programs of children with risk factors combined with continuous monitoring by family members, pediatrician and teachers are the foundation of the follow-up audiological post-screening in child age. In particular, the guidelines of JCIH 2007 assert that the timing of follow-up for children with risk factors should be structured and individualized in relation to the possibility of a possible progressive deafness or a late onset. Children who pass the neonatal screening but have a risk factor should be received at least one diagnostic audiologic evaluation between 24-30 months of age. Early and more frequent evaluations are recommended for children infected with cytomegalovirus (CMV), trauma, postnatal infections associated with sensorineural hearing loss, extracorporeal membrane oxygenation (ECMO) chemotherapy, a family history of childhood hearing impairment, verbal perception, language development or developmental delays. Any child who demonstrates delays in the development of auditory skills and/or communication should be submitted to an audiological evaluation to rule out hearing loss, although it has passed newborn screening [22]. In the presence of the above mentioned risk factors of the child is normally subjected to audiologic visit every six months until the third year of life and then annually for the next three years. It is also imperative that the family pediatrician, during health assessments, investigate the proper achievement of the main stages of auditory development and the acquisition of language.

It seems appropriate to identify some forms of SNHL insurgents in the postnatal period, such as: 1) the auditory deficits in subjects with no past history of audiological risk factors; 2) cases in which the family unit is not careful in reporting the risk factors related to the little patient and not to do perform audiological visits recommended or is not vigilant to acknowledge behavioral abnormalities secondary to a hearing impairment, particularly when grade mild; 3) disputes about the actual association of some of the risk factors identified by JCIH (2007) and the development of SNHL.

In 2012 Beswick et al. published the results of a work done to evaluate the effectiveness and the limits of a surveillance program post-audiological screening in children with risk factors. The study included 261.328 infants undergoing neonatal hearing screening in two steps by AABR, of which 7320 subjects were selected results "PASS" bilaterally and have at least one risk factor. These individuals were included in a follow-up program of audiology as follows: patients with a family history of congenital SNHL were subjected to TEOAEs,

Tympanometry and Visual Reinforcement Audiometry (VRA) to 6, 12, 18, 24 and 36 months life while patients with infection feedback to ABR to 3 months of life and then to 6, 12, 18, 24 months; patients with other risk factors were revalued using TEOAEs, Tympanometry and VRA to 9 or 12 months of life. The main audiological risk factors highlighted in the study population were: family history (40.5%), low birth weight (31.6%) and assisted prolonged mechanical ventilation (25%). In 56 subjects of 2107 (2.7%), with an average age of 22.7 months it was diagnosed with postnatal hearing loss, mainly sensorineural (64.3%), bilateral (76.8%) and mild (50%). Despite the achievement of an important objective, which the early diagnosis of a number of cases of post-natal SNHL, the authors have highlighted some limitations arisen from the application of a “audiological monitoring program targeted” structured. First and foremost is the high percentage of children, more than 20% of the total, who have not attended any of the events planned by the Protocol, in particular those belonging to the indigenous population ($p < 0.001$) and individuals with a single factor risk ($p < 0.001$), indicator of a heterogeneous distribution of audiology services in its territory and incorrect or missing information on campaigns [23].

Watkin et al., studying the prevalence of SNHL (3.65/1000) in a cohort of 35668 followed from birth until completion of the first year of primary school, they identified 57 cases of postnatal SNHL of which 20 to late-onset (0.56/1000) [24].

A possible screening system in pre-school children was proposed by Wu et al. who tested on 6288 children aged between 3 and 6 years a system called “Smart Hearing Screening”, which uses tablet devices to perform an behavioral audiometric test investigating the 1-2-4 kHz frequencies for pure tones between 20-60 dB HL. Among 463 subjects results “REFER” and then sent at tertiary center, 12 cases of SNHL (1.91/1000), demonstrating high specificity (92.6%) and a low sensitivity (37.5%). This screening system has some advantages: equipment used is cheap respect to audiometers, software processes directly response of patients, and is particularly valuable in subjects until four years, because of their greater capacity to complete the test independently.

Conversely, the use of questionnaires as possible audiological screening tool in the Primary epoch is still debated, because, although inexpensive, does not have that degree of accuracy and efficiency that they can be introduced on a large scale [25]. This is underlined by Bu et al. and Muñoz et al. who subjected, respectively, 317 and 4616 children screened in two steps by means of questionnaires and subsequent audiometric test, showing a low correlation between the results of the first and the presence of a hearing impairment [26, 27].

CONCLUSION

The analysis of recent literature shows the efforts made by research in the identification of a follow-up audiological system that can, in association with the newborn hearing screening, allowing early diagnosis of SNHL in childhood. However it is clear that some of the main characteristics that it should have, such as population “target”, the timing of assessments and instrumental investigations still do not find a common consent. It is well evident that an audiological monitoring program should cover all children, given the high rate of cases found no risk factors among patients with hearing loss results; monitoring should also ensure supervision in the early years of life and given the possible following onset of

deafness. Finally, the means and resources employed should have a high accuracy in identifying suspected cases without selecting an excessive number of false positives reducing the cost of audiological centers.

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Chapter 14

ENDOTHELIAL DYSFUNCTION, MICROVASCULAR DISEASE AND SENSORINEURAL HEARING LOSS

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ABSTRACT

The Stria Vascularis of the inner ear represents a fundamental element to ensure the endolymphatic homeostasis and, consequently, the regular function of the auditory-vestibular system [1]. In particular it allows electrolytes and metabolites exchange, in order (i) to preserve the inner ear fluids osmolality, and (ii) to protect the inner ear neuroepithelium from toxicity [1]. Reactive oxygen species (ROS) are considered responsible of inner ear cells damage and, as a consequence, of sensorineural hearing loss (SNHL); they act through (i) a direct cell metabolic damage, but also (ii) causing endothelial dysfunction and inducing apoptosis in cochlear neuroepithelial cells [2]. In the last decades, many Authors have investigated the role of cochlear microvascular disease and endothelial dysfunctions as a possible cause of SNHL. Cardiovascular risk factors (such as diabetes mellitus, hypertension, hypercholesterolemia, hyperhomocysteinemia et al) have been reported to be associated to an increased risk of endothelial dysfunction and microangiopathy in the inner ear. These mechanisms have also been proposed to be involved in the pathophysiological process of idiopathic sudden sensorineural hearing loss (SSNHL) [3].

Aim of this chapter is to review the etiopathogenetic mechanisms of the cochlear endothelial dysfunction and of the cochlear microvascular disease and their links to sensorineural hearing loss.

Keywords: sensorineural hearing loss, sudden sensorineural hearing loss; reactive oxygen species, endothelial dysfunction, microvascluar disease.

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INTRODUCTION

Endothelial factors play a fundamental role also in the cochlear function. The endothelial tissue is responsible of the balance between proaggregant and antiaggregant factors, produces vasodilator factors, such as nitric oxide (NO), and can be influenced by the vasoconstrictor effect of angiotensin II or endothelin [4]. Furthermore, in the endothelial structure, there is a reserve of proinflammatory interleukins, which can be released in case of stimulation by vascular, mechanical and metabolic risk factors [5]. Also pericytes and myocytes, surrounding endothelial cells, can release vasoactive substances (such as histamine, serotonin, prostaglandins) involved in the microvascular autoregulation, also according to the local metabolic requirements. Different studies assessed the importance of NO in increasing cochlear blood flow and in protecting inner ear in some stressful conditions; in fact, NO production seems to be incremented during ischemia, ototoxicity and endolymphatic hydrops [6].

The cochlea lateral wall and, in particular, the Stria Vascularis (SV), is responsible for the endolymph production and for the maintenance of cochlear fluids electrochemical balance. This is necessary in order to generate the endocochlear potential and, as a consequence, to the correct auditory function [7]. SV is a complex epithelial structure, made of three layers with different cells (marginal, intermediate and basal cells), and provided by a terminal capillary bed. It is a vascularized epithelial tissue with a great oxygen requirement, due to the high metabolic activity of hair cells. This condition makes the inner ear vulnerable to ischemic events [8]. Also, SV is very sensitive to variation of blood viscosity, therefore each modification of haematocrit, plasmatic viscosity, cellular and platelet aggregation and red cells deformability could have a repercussion on the SV function and, as a consequence, on the endolymphatic homeostasis [9].

The inner ear vascularization is supplied by the internal auditory artery (also known as labyrinthine artery), an anterior inferior cerebellar artery branch [8]. The anterior vestibular, the vestibulocochlear and the main cochlear arteries are the terminal branches of labyrinthine artery. Thus, the cochlear blood supply is a terminal capillary bed and this makes the cochlea very sensitive to vascular accidents, as there are no other collateral vessels [8].

Furthermore, SV is a blood-labyrinth barrier, which represents the principal element for the protection of inner ear from toxic substances conveyed from blood through cochlear vessels [10]. The physiological mechanisms of regulation of intrastrial fluid-blood barrier permeability are still not completely known, but para-cellular and transcellular pathways have been proposed to be involved in the control of vascular permeability as much as basement membrane alteration [7].

SENSORINEURAL HEARING LOSS AND ENDOTHELIAL DYSFUNCTION

Sensorineural hearing loss (SNHL) is a hearing function disorder caused by loss of cochlear hair cells and/or neurons of the spiral ganglion and/or of the central auditory pathway. Generally, the damage of inner ear cells is irreversible and it is associated to a permanent SNHL. There are many factors capable to injury cochlear cells: age, noise, ototoxic drugs (such as aminoglycosides, cisplatin and furosemide) or infections [2]. It has

been stated that also a SV dysfunction could be involved in damaging the cochlea, considering its important role of intrastrial fluid-blood barrier, which physiologically protect inner ear from blood toxic substances [7]. Since inner ear cells are very sensitive to minimal changes of blood flow, an impaired SV microvascular perfusion could impact on hair cells. A cochlear microvascular disease could be related to a systemic microangiopathy due to traditional cardiovascular risk factors (such as hypertension, hyperlipemia, diabetes mellitus, etc.) [11, 12].

Diabetes mellitus is a well-known prevalent chronic systemic disease, characterized by an incremented blood sugar level. Some of its complications are related to vascular damage (macro and micro -angiopathy, such as retinopathy, nephropathy and neuropathy), due to endothelial indirect dysfunction or direct cellular damage: advanced glycation end-product (AGE) creation, polyol and hexosamine metabolic pathway and protein kinase C activation [13]. Diabetes predisposes to precocious and more frequent atherosclerosis compared with healthy population [9] in labyrinthine vascularization as well as in other peripheral capillary beds [14]. Few studies in literature investigated among the specific role of diabetes in the pathophysiology of SNHL. Rust and coworkers assessed that hyperglycemia and glucose intolerance genetic-based in type 2 diabetes could be associated to an inner ear alteration due to the loss of outer hairy cells [15]. Also Frisina, in 2006, reported diabetes to damage inner ear function in older patients affected by presbycusis [16].

Presbycusis itself could be related to age-related microvascular disorders [17]. In the elderly, the loss of cochlear neuroepithelial cells, but also of spiral ganglion neurons, are secondary to alterations of the local blood flow, systematic degeneration of endothelial tissues and a reduction of antioxidant factors (such as glutathione) [18]. In human temporal bone studies, atrophy of SV, thickened basement membrane and deposits of immunoglobulin and laminin in strial vessels have been found in these patients [7]. It is also widely accepted that aging is due to accumulated oxidative tissue injuries and to increased ROS production. In particular, an incremented production of ROS is reported during hypoxia and it may impact mitochondria in the apoptosis process [6]. Also in the aging inner ear, an increased ROS concentration and a decrease antioxidant functions are responsible of mitochondrial DNA mutations and, as a consequence, of a reduction of the energy production and consequent cochlear damage [17, 2, 19]. The oxidative stress theory for the onset of SNHL has been described in only few studies, in which Authors demonstrated the correlation between inner ear disease and endothelial dysfunction caused by increased production of ROS [20, 21, 22, 23]. Reactive oxygen species (ROS) can act through (i) a direct cell metabolic damage, but also (ii) causing endothelial dysfunction and inducing apoptosis or necrosis in cochlear neuroepithelial cells [2].

The principal source of ROS in the inner ear could be located in hair cells mitochondria; however, also cytoplasmatic enzymes such as NADPH oxidase and xanthine oxidase have been reported to be responsible of ROS production. Nevertheless, also high blood concentration of ROS may lead to direct cochlear cellular death, because of their direct oxidizing effect on cellular lipids, proteins and DNA, as well as due to their negative effect on endothelial cells. ROS and, particularly, hydrogen peroxide, may act on endothelial cells and activate cellular apoptosis pathways through apoptosis signalling kinase 1 (ASK1) and c-Jun N-terminal kinase (JNK) [24]. The subsequent endothelial dysfunction could contribute to the pathogenesis and maintenance of vascular diseases and, therefore to cochlear damage.

Oxidative stress represents also the pathogenetic mechanism of noise-induced SNHL: a prolonged exposition to noise determines an increased production of ROS and a capillary vasoconstriction of the basilar membrane, spiral ligament and SV [7]. Furthermore, it has also been reported that an increased vascular permeability, leukocytes aggregation, endothelial cells injury and structural and molecular alterations in the blood-labyrinth barrier can be present in mouse inner ear, after acoustic trauma. This finding indirectly supports a microvascular disease and endothelial dysfunction as pathogenetic mechanism of SNHL [7]. Also some autoimmune diseases can determine a progressive SNHL onset and the pathogenetic mechanism proposed involves stria vessels as target of autoantibodies (e.g., immune-complexes deposition) [25].

SUDDEN SENSORINEURAL HEARING LOSS AND ENDOTHELIAL DYSFUNCTION

Sudden sensorineural hearing loss (SSNHL) is an acute hearing disorder involving at least 3 consecutive frequencies over a 72-h period [26]. Only in few cases is possible to demonstrate an aetiological agent (7-45%) [27], and the remaining cases are therefore classified as idiopathic [28].

Many etiopathogenetic hypothesis have been proposed: viral infection [29, 30], immune-mediated damage [31, 32], injury / rupture of cochlear labyrinthine membranes [33, 34] and inner ear vascular disease [35]. The latter has been proposed particularly considering the terminal arterial supply of the inner ear [8]. It has been hypothesized that (i) either a micro-thromboembolism, (ii) either a micro-haemorrhage (iii) either a vascular spasm of the labyrinthine artery could be responsible of cochlear damage therefore inducing a SSNHL [36]. Furthermore, this theory could be supported by the fact that in systemic conditions characterized by microvascular dysfunction (such as atherosclerosis, hypertension, diabetes mellitus, polycythemia, bacterial endocarditis...), SSNHL is generally reported to be more frequent. In a case-control study, Aimoni and coworkers [37] reported a significant correlation between SSNHL and cardiovascular risk factors, such as diabetes (especially if insulin-dependent) and hypercholesterolemia, suggesting that these factors are correlated to a higher risk to develop a SSNHL. Marcucci et al. [9] found that incremented blood levels of homocysteine and plasminogen activator inhibitor-1 (PAI-1) and the presence of anticardiolipin antibodies are associated to SSNHL. Hyperhomocysteinemia is considered a major cardiovascular risk factor, as well as PAI-1 as the major factor inhibiting fibrinolytic system (and then, in an increased concentration, it represents an important pro-thrombotic factor), as well as anticardiolipin antibodies [9]. With their study, these Authors indirectly supported the vascular etiopathogenetic theory of SSNHL.

Quaranta and coworkers [3] and Haubner and collaborators [38] assessed the role of endothelial dysfunction of the cochlear microcirculation in the development of SSNHL, showing an increased concentration of circulating VCAM-1 (vascular cell adhesion protein 1) in SSNHL patients, as a confirm of a vascular involvement in SSNHL development [39].

Moreover, according to Merchant's stress response theory [40]: inflammatory cytokines could activate intracellular oxidative pathways of cochlear neuroepithelium, involving

transcription factors (such as NF κ B). This aberrant activation can damage the cochlear homeostasis and could be related to the development of a SSNHL.

Even though the vascular hypothesis for SSNHL could be very plausible, to day, the question is still debated [9, 6, 29, 37, 41]; in particular cardiovascular risk factors have also been reported to play a controversial role in SSNHL threshold recovery [37, 42].

Also an inner ear electrolytic imbalance has been investigated as a possible pathogenetic mechanism [43]. A sudden electrolytic disorder of the inner ear could explain either the rapid onset of sensorineural hearing loss, either the hearing threshold recovery (partial or complete) [44, 45]. According to this theory, an etiologic agent could impact the inner ear neuroepithelium function indirectly, acting on metabolic function of the inner ear structure involved in the electrolytes transport (cochlear lateral wall) [43, 45, 46]. Therefore, a cochlear lateral wall damage could impact the ionic (Na⁺, K⁺, Fe²⁺, Cl⁻) transport between blood and endocochlear fluids and, for this reason, could be associated to a sudden hearing impairment [43, 47].

Furthermore, it is well known that inner ear is particularly sensitive to pH levels and that its reduction could lead to hearing loss [48]; for this reason, an acute damage of the cochlear lateral wall, implicated in the cochlear pH maintaining, could be responsible of a SSNHL development.

CONCLUSION

Disruption of blood-labyrinth barrier, cochlear microvascular disease and endothelial dysfunction could be involved in the pathogenesis of SNHL. Oxidative stress theory could represent a possible pathogenetic mechanism of cochlear injury, and ROS could act through (i) a direct hair cells metabolic damage and (ii) also causing endothelial disorder, inducing, as a consequence, apoptosis in cochlear neuroepithelial cells [2].

Cardiovascular risk factors, such as diabetes mellitus, hypertension, hypercholesterolemia, hyperhomocysteinemia, have been found to be associated to an increased risk of microvascular inner ear disorder [9, 37, 29, 36]. To date, there are few diagnostic possibilities to assess inner ear lesions in patients affected by SNHL. Recent improvements in imaging techniques, such as magnetic resonance imaging with specific contrast agents, could offer interesting prospective in order to study cochlear structural, functional, metabolic and also vascular permeability features [7]. More studies are necessary in order to understand the relationships between inner ear injury, endothelial dysfunction and micro-vascular disorders also in order to develop new potential diagnostic and therapeutical interventions.

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Chapter 15

SUPEROXIDE DISMUTASE AND SENSORINEURAL HEARING LOSS

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ABSTRACT

Superoxide dismutase (SOD) is an antioxidant agent that can be found in almost every cell exposed to oxygen. It is responsible for the dismutation of superoxide anions resulting from cellular metabolism into oxygen and hydrogen peroxide. In particular, superoxide dismutase (SOD), in its cytoplasmic isoform, contains copper (Cu) and zinc (Zn), and can be found in cochlear tissue (stria vascularis, spiral ligament, spiral ganglion neurons and organ of Corti). The antioxidant function of SOD is important for protection of the inner ear cells from toxic substances, such as reactive oxygen species (ROS). The role of SOD has been investigated in noise-induced hearing loss and in presbycusis, whereas elevated concentrations of ROS are responsible for inner ear damage. In the last decades, many authors have tested the protective role of SOD in the cochlea of animal models. Recently, the role of SOD gene polymorphisms in the susceptibility of sudden sensorineural hearing loss has been investigated as well.

The aim of this chapter is to review the role of SOD in the cochlear metabolism and its involvement in the pathogenesis of noise induced hearing loss, age related hearing loss and sudden sensorineural hearing loss.

Keywords: sensorineural hearing loss, superoxide dismutase, reactive oxygen species, oxidative stress, noise-induced hearing loss, presbycusis

INTRODUCTION

The oxygen metabolism represents the fundamental engine for aerobic cells, which is necessary for the cellular production of energy. Reactive oxygen species (ROS), such as

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hydrogen peroxide, superoxide and hydroxyl radical, are chemically reactive elements obtained as a normal product of the oxygen metabolism and play an important role in cellular homeostasis and signalling [1]. In a standard cellular environment, ROS oxidant activity is counterbalanced by an antioxidant system, which represents the cellular antiradical defence, including some molecules such as glutathione peroxidase, catalase, vitamin A, C and E and superoxide dismutase (SOD) [2].

Several conditions, such as exposition to ionizing radiation and inflammatory processes, may determine an augmented production of ROS, configuring a so-called 'oxidative stress' status. In such circumstances, a loss of balance between oxidant and antioxidant agents occurs and the excessive ROS concentration can cause cellular damage. The mechanisms, through which incremented ROS levels may cause cellular injury, are well established: lipid peroxidation, protein oxidation and DNA damage. These mechanisms are also able to induce cellular death through necrosis or apoptosis [1].

Oxidative stress is known to be involved in the normal ageing process [3]; also, it is known to play a pivotal role in the pathogenesis of different diseases, such as carcinogenesis [4], ischaemia [5] and neurodegenerative disorders, including Alzheimer disease [6]. Furthermore, it has been reported that oxidative stress may be linked to hearing loss [7]: incremented ROS levels, among inner ear cells, have been reported in several conditions such as presbycusis [8], ototoxicity (i.e., cisplatin, aminoglycosides) [9] and noise exposure [10]. Inner ear hair cells are particularly susceptible to variation of cochlear blood flow and to oxygen levels [11]. Moreover, the cochlear lateral wall (stria vascularis and spiral ligament), involved in the preservation of the endolymphatic homeostasis and the endocochlear potential, is particular vulnerable to ischemic conditions [12].

It has been described that in case of cochlear ischemic injury, an increased ROS production may determine inner ear cells damage through two mechanisms: (i) a direct cell metabolic impairment and (ii) an endothelial dysfunction [13]. Some authors [14,15,16,17] have also linked oxidative stress to the onset of sensorineural hearing loss (SNHL), describing a correlation between ROS-induced endothelial dysfunction and inner ear disease.

In this scenario, SOD represents an important defence system against oxidative stress in the inner ear.

SUPEROXIDE DISMUTASE AND THE INNER EAR

SOD is a cellular oxidoreductase enzyme involved in the dismutation of the superoxide into hydrogen peroxide. SOD is a crucial cellular antioxidant element, which can be found in almost every cell exposed to oxygen [18]. In mammals there are three isoforms of SOD: they differ mainly in the ion included in the active site (copper, iron, zinc, nickel and manganese) and in their distribution: SOD1 is located in the cytoplasm, SOD2 in mitochondria, while SOD3 is an extracellular form [18].

During the last decades, many authors have already demonstrated the crucial importance of the oxidoreductive function of SOD with animal models. Mice lacking SOD activity develop several pathologies, such as hepatocellular carcinoma [19], early cataract [20], and also hearing loss [21]. Furthermore, other authors have demonstrated the protective role of SOD towards outer hair cells *in vitro* [22] and in the mice cochlea [23].

SOD1, the cytoplasmic isoform, has been found prevalently in cochlear tissue (stria vascularis, spiral ligament, spiral ganglion neurons and organ of Corti), with a minor concentration also located in the mitochondria intramembrane space [24,25]. Stria vascularis retains high SOD concentration, as it is involved in the maintenance of the endocochlear potential due to its central role in ionic transportation; in addition, this process requires a continue active aerobic oxidation in order to obtain ATP [12]. High SOD concentration in stria vascularis plays a relevant role in detoxification from oxygen free radicals [25]. In spiral ganglion neurons and in the organ of Corti, SOD has been reported to protect directly neural and hair cells from ROS damages as well [21].

SUPEROXIDE DISMUTASE AND NOISE-INDUCED HEARING LOSS

The pathogenic role of oxidative stress in noise-induced hearing loss has been already described [26]; increased levels of ROS after noise exposure have been linked to hair cells damage [27]. Recently, Fetoni et al., [10] demonstrated the morphological and functional alterations of hair cells and spiral ganglion neurons after a repeated noise exposure in a rat model: they described a cochlear damage, at the medial and basal parts, with a consequent hearing loss as showed by an increased ABR thresholds. This phenomenon was due to an oxidative imbalance, described by the Author as an increase in the cellular production of superoxide and the consequent lipid peroxidation. They also observed an amendment of cochlear injuries and of the auditory thresholds, following the administration of an antioxidant treatment to reverse the noise-induced redox unbalance.

In 1999, Ohlemiller et al., demonstrated an augmented susceptibility to noise-induced hearing impairment in a group of mice lacking SOD1 [28], highlighting the defensive significance of intracellular controlled levels of SOD.

Liu et al., [29] explored the relationship between SOD1 polymorphisms and the susceptibility to noise-induced hearing loss, describing a significant difference between noise-resistant and noise-sensitive workers. In particular, they suggested that rs2070424 and rs10432782 SOD1 polymorphisms might be responsible for an increased susceptibility to noise-induced hearing impairment. A more recent meta-analysis performed by Wang et al., [30] examined the same relationship, considering a specific SOD2 polymorphism (c47t): in this study, the authors did not find any statistically significant correlation.

SUPEROXIDE DISMUTASE AND PRESBYCUSIS

Oxidative stress is already known to be involved in the aging process; an unbalanced cochlear redox status also plays an important role in the development of presbycusis. A reduction of SOD enzymes levels (especially SOD2) in aged tissues of rats and mice has been comprehensively described more than 30 years ago [31, 32]. The relationship between oxidative stress and the aging of inner ear was investigated in mice [8]: oxidative stress levels in the aging cochlea increase, while antioxidant factors, such as mitochondrial apoptosis-inducing factor and SOD2, decrease. In particular, it has been found that SOD2 levels are

reduced in outer hair cells, supporting cells and spiral ganglion cells. McFadden et al, in 1999, demonstrated that in a group of SOD1 lacking mice, the loss of inner ear outer hair cells was greater than in the control wild type mice group, highlighting that the deficiency of SOD activity enhances the age-related degeneration of neuroepithelium of the inner ear [21]. These results are consistent with the study performed by Keithley et al., in a mice model in 2005 [33].

SUPEROXIDE DISMUTASE AND SUDDEN SENSORINEURAL HEARING LOSS

Genetic alterations of SOD enzymes have been associated with several diseases; for example, mutations of SOD1 can cause familial amyotrophic lateral sclerosis, a form of motor neuron disease [34]. Different authors examined the role of SOD gene polymorphisms in hearing loss development [29, 30], which appears to be race-specifically distributed. More recently, Kitoh et al., explored the potential correlation between a particular polymorphism of SOD1 gene and the susceptibility to sudden sensorineural hearing loss (SSNHL) [35].

There are many proposed classical etiological theories of SSNHL, including the vascular hypothesis, based on a hemorrhagic or ischemic insult to cochlea [36]. Considering this possible etiology, ROS may represent an important factor in cochlear damage and sudden hearing loss. The relation between SOD genetic polymorphisms and SSNHL has not been largely investigated yet. Kitoh et al., [35] found in SOD1 rs4998557 a polymorphism likely associated with susceptibility to SSNHL, however no SOD2 polymorphisms were found to be correlated with a predisposition to SSNHL. Earlier, Teranishi et al., [37] explored the SOD2 polymorphism in two groups of patients, one group of patients with SSNHL and another group of patients with Ménière's Disease. They found no statistically significant differences in the distribution of polymorphisms among the two groups. In conclusion, they did not suggest any association between specific genotypes and incremented risk of SSNHL or Ménière's Disease. Nonetheless, they described a particular C allele of SOD2 (rs4880) to be associated with progression of the hearing impairment in Ménière patients.

CONCLUSION

SOD represents an important protective antioxidant system of eukaryotic cells. In the cochlea, SOD seems to play a crucial role in protecting auditory neuroepithelium against toxic substances, such as ROS.

A possible 'therapeutic – protective' role of increased SOD levels has been described. Nonetheless, it has been reported that an over expression of SOD1 in mice does not protect inner ear cells from age-related or noise induced damage [33,38]; however, some authors demonstrated a potential protection provided by SOD against ototoxicity induced by antibiotic drug administration (kanamycin) in mice [23] and in guinea pigs [39].

Recently, Serra et al., [40] proposed a brand-new application of SOD as a nutraceutical treatment in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS), a condition

known to be associated with oxidative unbalance. However, a similar approach to inner ear disease treatment has not been previously suggested to our knowledge.

So far, the role of SOD in the pathogenesis of inner ear diseases remains an unresolved issue. Since SOD is involved in hearing function and protection, it could represent a possible therapeutic target for certain inner ear diseases.

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Chapter 16

CARDIOVASCULAR RISK FACTORS AND SENSORINEURAL HEARING LOSS

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ABSTRACT

The inner ear may be impaired by vascular affections since it is supplied by a terminal blood flow and has a sustained metabolic activity [1]. It has been reported that the function of labyrinthine vessels can be influenced by several local factors such as perivascular sympathetic innervation, arterial systemic blood pressure and labyrinth liquids pressure ratio, antidiuretic hormone receptors, endothelial dysfunction and ionic transport mechanisms [2].

A possible link between microvascular inner ear disease and sudden sensorineural hearing loss (SSNHL) has been proposed: a sudden labyrinth oxygen lack may be responsible for acute inner ear damage, involving hair cells and then affecting hearing or vestibular function [3]. Moreover, a primary autonomic vascular dysregulation has been related to acute cochlear damage [2]. Many Authors have investigated the possible involvement of cardiovascular risk factors (i.e., hypertension, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia) in the pathogenesis of sudden sensorineural hearing loss [4]. Furthermore, microcirculation defects, frequently associated to atherosclerosis, have been reported to play a major role in the onset of acute cochlear damage [5].

The aim of this chapter is to review the relationship between cardiovascular risk factors, systemic circulatory diseases and inner ear disorders, particularly focusing on the involvement of cardiovascular factors in the pathogenesis of SSNHL.

Keywords: sensorineural hearing loss, sudden sensorineural hearing loss, cardiovascular risk factors, hypertension, diabetes mellitus, smoking

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INTRODUCTION

The inner ear is a sensorial organ characterized by neuroepithelial cells with a high oxygen-dependent metabolism. Its vascularization is provided by a terminal circulation: the labyrinthine artery is a branch of the anterior inferior cerebellar artery (rarely of the basilar artery directly) and it is the only vessel responsible for the inner ear blood supply [1]. This anatomic and functional configuration (in particular, the absence of collateral vessels and the sustained metabolic activity of the inner ear cells) represents the main reason for the high sensitivity of the inner ear to vascular accidents [1]. There are three terminal branches originating from the labyrinthine artery: (1) the anterior vestibular, (2) the vestibulocochlear and (3) the main cochlear artery, which supply different parts of the inner ear (vestibular and cochlear partitions) [1]. Towards the terminal extremity of these vessels, the arteries decrease in size and lose their muscular layers, therefore increasing their predisposition to peripheral vasomotion disorders [6]. This vascular subdivision represents the anatomical explanation for the different clinical features (matching hearing loss and vertigo) resulting from vascular accidents, such as localized ischemic events [7]. Therefore, alteration of platelet aggregation, red cells deformability, haematocrit and plasmatic viscosity (as described in several conditions such as leukaemia, leucocytosis, polycythaemia, sickle-cell anaemia, cryoglobulinemia, macroglobulinemia) may have implications also on inner ear function [8].

There are several local factors influencing the inner ear perfusion, such as perivascular sympathetic innervation, arterial systemic blood pressure or labyrinthine liquids pressure ratio [2]. The labyrinthine blood flow is also regulated by blood labyrinthine barrier, pericytes, smooth muscle cells and fibrocytes; endothelial dysfunction and alterations of ionic transport could represent another mechanism of cochlear injury, as well [9].

Concerning the autonomic nervous system control on local inner ear perfusion [10, 11], the function of distal arterioles has been reported to affect directly the number of perfused capillaries and the partition of local blood distribution. In particular, many studies have focused on stria vascularis capillaries and on their capacity to interact with different signals, such as iron ions and nitric oxide in presence of an acoustic stimulus, then determining an increase of local blood flow [12].

Alterations of the intracranial venous circulation have been related to the pathogenesis of inner ear disorders, in consideration of the delicate balance existing between intracranial and labyrinthine fluids pressure; it has been reported that a variation of venous pressure may interfere with inner ear homeostasis [13, 14, 15].

SENSORINEURAL HEARING LOSS AND CARDIOVASCULAR RISK FACTORS

The inner ear may be damaged by hemodynamic or metabolic events in case of systemic diseases, such as cardiovascular, renal, inflammatory, autoimmune and/or metabolic disorders [16]. Hearing loss has been related to cardiovascular risk factors (such as male gender, hypertension, dyslipidaemia, obesity, lack of physical activity, diabetes mellitus, atherosclerosis, smoking) and also, in the Framingham Heart Study, to cardiovascular events, such as cerebrovascular and coronary artery disease [16, 17, 18]. In addition, other cardiovascular risk factors, such as body mass index, waist circumference and socioeconomic

status, have been found to be linked to the incidence of hearing loss in longitudinal studies [19, 20, 21].

Obesity has been considered to cause inner ear cells injury through ischaemic damage and oxidative stress, the same mechanisms through which tobacco, potentially, could act as risk factor for hearing loss [21].

High systolic blood pressure (more than the diastolic) was found to have a positive correlation with hearing loss in frequencies above 500Hz [22].

Increased blood sugar levels may damage the vascular endothelial walls. Moreover, an increased prevalence of hearing loss has been reported in patients with an impaired glucose control [23]. In 2006 Fukushima demonstrated a condition of angiopathy and degeneration of outer hair cells and of stria vascularis examining temporal bones of diabetic patients [24].

Elevated lipid blood levels (low-density lipoproteins in particular) have been linked to microvascular damage [25], nonetheless a direct association between blood lipids and hearing loss has not been demonstrated yet [26].

Recently, the relationship between hearing loss and levels of serum C-reactive protein (CRP), another cardiovascular risk marker, has been investigated; Nash [27] found an increased 10-year risk of hearing loss in case of high levels of CRP [26], but further confirms are necessary.

Subclinical atherosclerosis has been related to an increased incidence of hearing loss in a large cohort study (1984 middle-aged patients - increased risk of about 15%) [28]. Atherosclerotic plaques may affect inner ear perfusion due to a decreased availability of oxygen and nutrients to the cochlea [22]. In 1978, Makishima found a positive association between (i) the narrowing of the internal auditory artery, (ii) stria vascularis atrophy, and (iii) hearing loss, suggesting that a spiral ganglion atrophy could result from a chronic reduction of cochlear blood flow caused by atherosclerosis [29]. However, the precise role of atherosclerosis, as a risk factor for hearing impairment, has not been completely understood [17], since systemic atherosclerosis may also coexist with a normal hearing function [30].

Presbycusis is among the most frequent sensorial deficit in elderly and its prevalence increases with age, as much as cardiovascular diseases [31]. Since cardiovascular risk factors are generally more frequent in the elderly, it could be difficult to distinguish the effects of cardiovascular diseases on inner ear function, from those related to (i) ageing, (ii) occupational or environmental noise exposure, or (iii) use of ototoxic drugs [17, 32].

The interaction between presbycusis and diabetes mellitus has been investigated [33]. Frisina studied a population of aged diabetic patients compared to age-matched healthy control patients, performing both peripheral and central auditory tests [33]: the Author evidenced significant differences between the two groups in both auditory categories tests with poorer performances in the diabetics group, highlighting that hyperglycemia may damage not only the inner ear cells, but also the central nervous system.

SUDDEN SENSORINEURAL HEARING LOSS AND CARDIOVASCULAR RISK FACTORS

To date, the pathogenesis of idiopathic sudden sensorineural hearing loss (SSNHL) remains unclear. Among the different etiopathogenetic hypotheses, the vascular theory is one

of the most investigated [6, 34]. Several Authors evaluated the existence of a link between cardiovascular factors and the onset of sudden hearing loss [7, 8, 35]. Marcucci [8] and Capaccio [36] found an increased concentration of cholesterol, fibrinogen and homocysteine as cardiovascular risk factors in patients affected by SSNHL. In addition, several inherited and acquired cardiovascular risk factors have been found to increase the risk of hearing impairment development: Ballesteros [35] found a higher prevalence of the 807T thrombophilic polymorphism of platelet glycoprotein Ia/IIa in patients affected by idiopathic SSNHL compared to healthy control patients and assessed a poorer hearing recovery rate in patients homozygous for this polymorphism.

Aimoni *et al.* [4] evidenced hypercholesterolemia and diabetes mellitus (particularly associated with insulin therapy) to be significantly more frequent in patients affected by SSNHL and, later, Chang [25] found the same two issues to be independent risk factors for SSNHL, even if some conflicting data exist [37].

Mosnier [7] did not find any significant difference in the prevalence of cardiovascular risk factors (such as total lipids, diabetes mellitus, and smoking) among patients with SSNHL and the healthy controls, whereas reported that cardiovascular accidents (including myocardial infarction, stroke, transient ischemic attack) were significantly more prevalent in patients with SSNHL.

In a case-control study, Ciccone *et al.* [38] found a significant lower flow-mediated dilation of the brachial artery and significant higher total cholesterol and low density lipoprotein cholesterol blood levels in patients affected by SSNHL compared to the healthy control group, suggesting a possible correlation between idiopathic SSNHL and vascular endothelial disorder. Previously, Balletshofer [39] found that 5 out of 6 patients affected by idiopathic SSNHL showed endothelial dysfunction, supporting an involvement of microcirculation disorders in the pathogenesis of hearing impairment.

In a large cohort-control study, a higher risk of stroke (1.64 rate) has been estimated in patients with idiopathic SSNHL [40].

Keller [41] found an association between acute myocardial infarction and previous onset of SSNHL; Lin [42] defined SSNHL as a possible independent risk factor for myocardial infarction, in particular for patients aged ≥ 50 years. These observations may allow considering SSNHL as a possible predictor of major cardiovascular accidents [40, 41, 42].

In 2015, Pirodda speculated a possible involvement of a primary autonomic vascular dysregulation in the acute cochlear damage [43]. The primary vascular dysregulation syndrome, a condition of inappropriate vasoconstriction and vasodilatations of arteries, veins and capillaries, has been previously associated to several ophthalmological diseases [44]. In this syndrome low blood pressure, minor resistance to psychological stress, major sensitivity to pain, autonomic imbalance, migraine are often present [44] and have been linked also to the onset of a labyrinthine acute impairment [43]. Schulz and co-workers showed an altered autonomic regulation in patients affected by idiopathic SSNHL, particularly demonstrating modifications in their blood pressure regulation, in comparison to normal hearing patients [45, 46, 47]. Hultcrantz and collaborators [10] supposed that in case of reduced cochlear blood flow (i.e., in case of hypotension), cochlear circulation could depend on sympathetic tone.

The involvement of cardiovascular risk factors in the pathogenesis of idiopathic SSNHL seems to be plausible, but remains a hypothesis to date. The role of cardiovascular risk factors in hearing threshold recovery after a SSNHL is also unclear [48].

CONCLUSION

Micro-vascular defects can damage the inner ear, since it is a sensory-neural organ with a sustained metabolic activity, supplied by a terminal blood flow [1]. Many Authors have investigated the role of cardiovascular risk factors in the pathogenesis of hearing loss and, in particular, of idiopathic SSNHL [16-30, 34]. Even if, to date, clear evidences do not support the vascular etiopathogenetic hypothesis, it is possible to consider hearing disorders as a potential sign of circulatory instability [2, 21]. In this regard, there are also evidences supporting links between SSNHL and major cardiovascular diseases such as stroke [40, 41, 42]; a careful evaluation of cardiovascular risk factors should be recommended among these patients [21, 49].

For these reasons, in case of hearing impairment, Audiologist and Otolaryngologist should (i) investigate patients cardiovascular history, (ii) refer for blood tests, electrocardiogram and supra-aortic trunks ultrasound, (iii) possibly refer to a cardiologist for further diagnostic investigation and (iv) encourage patients to reduce modifiable cardiovascular risk factors.

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Chapter 17

AUDIOLOGY, HEARING AIDS AND COCHLEAR IMPLANTS

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HEARING

- In 2008, MarkeTrak, a well-known research group estimated that 1/10 individuals complain of hearing loss.
- In 2012, the World Health Organization (WHO) estimated that 1/3 of individuals over the age of 65 had significant (i.e., >40 dB HL) hearing loss; 17% of those individuals lived in the USA.
- In 2014, researchers from the U.S. National Center for Health Statistics reviewed self-reported hearing health data from the National Health Survey and found that hearing problems were reported by 43% of participants over age 70 and by 19% of participants between the ages of 40-69. Men attributed their hearing loss to noise and women attributed their hearing loss to age.
- Age-related hearing loss (Presbycusis):
 - 23% chance of age-related hearing loss in men and women aged 60-69, and a 48% chance of age-related hearing loss in men and women aged 70-79.
 - In adults 50-69 years of age, greater threshold shifts occurred in the 3000-8000 Hz range. In adults 70-89 years of age, greater threshold shifts occurred in the 500-2000 Hz range.
 - Men typically have greater hearing loss as compared to women at all ages.

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- The rate of threshold shift in men aged 48-59 was 0.4 dB per year at 500 Hz and approximately 1.6 dB per year at 8000 Hz, while the reverse was true in men age 80 and above (i.e., 2.1 dB per year at 500 Hz and 1.05 dB at 8000 Hz).
- Despite the creation of the Occupational Safety and Health Administration (OSHA) in 1971, the occurrence of noise-induced hearing loss (NIHL) continues to be an issue in the United States. In 2010, the Bureau of Labor Statistics revealed that NIHL is the most commonly cited health condition among workers in manufacturing. Some facts pertinent to NIHL:
 - The approximate resonant peak frequency of the external ear canal is 2800-3000 Hz.
 - Damage from noise exposure typically occurs at a frequency approximately ½ octave above the frequency of the offending noise.
 - There is evidence that the middle frequencies of a broadband noise, as is typical of occupational noise, may be more hazardous to hearing.
 - The greatest shift in threshold typically occurs at or around 4000 Hz; however, it may also occur at adjacent frequencies of 3000 and 6000 Hz when the frequency composition of the noise is not broadband.
 - Damage is usually greatest during the first ten years of exposure.
 - OSHA requires employers to have a hearing conservation program when workers are exposed to a time-weighted average noise level $\geq$ 85 dBA in an 8 hour period (Table 1).

Table 1. OSHA Permissible Exposure Limits (29 CFR 1910.95)

Permissible Exposure Limit (TWA)	Maximum Exposure
90 dBA	8 hours
95 dBA	4 hours
100 dBA	2 hours
105 dBA	1 hour
110 dBA	½ hour
115 dBA	¼ hour

- In children, hearing loss is usually related to middle ear problems. Acute otitis media may occur at least once in approximately 80% of children before the age of 3, and at least three times in approximately 40% of children before the age of 3. Middle ear effusion may cause the following:
 - Hearing losses that range between slight (i.e., 16-25 dB) to moderate (i.e., 41-55 dB), dependent upon the level and viscosity of the middle ear effusion (MEE).
 - Greater hearing loss in the high frequency range.
 - A dampening of soft (i.e., 20-30 dB loud) high frequency speech sounds (i.e., /f/, /s/, /θ/) such that a child may find it difficult to recognize those sounds in conversational speech (i.e., 40-55 dB HL).

AUDIOLOGICAL EVALUATION: AIR AND BONE CONDUCTION

- The audiogram is a graph comprised of vertical and horizontal lines representing a) the frequencies most important for understanding speech (250-8000 Hz), and b) the decibel levels (-10 to 110 dB HL) at which said frequencies are heard by the individual being tested via either air conduction or bone conduction.
- Air conduction testing, with insert phones or headphones, reflects the total response of the hearing system, and is dependent upon the transmission of sound via the external ear, the tympanic membrane (TM), and the ossicular chain before it is delivered to the inner ear (i.e., cochlea/VIIIN/spiral ganglion).
 - The combined influences of the head, the pinna, and the ear canal can amplify sounds within the 2000-4000 Hz range as much as 10-15 dB.
 - Due to the difference in size between the TM and oval window, the leverage action of the ossicular chain (i.e., manubrium is 1.3 times longer than the arm of the incus) and the unique movement of the TM (i.e., more force on the umbo due to greater displacement of the TM on either side), the pressure exerted on the stapes/oval window is approximately 44:1. These effects result in an approximate 30 dB gain in sound pressure level at the stapes, which is necessary to overcome the dampening effect on sound being transmitted from the air-filled middle ear cavity to the fluid-filled cochlea.
- Bone conduction testing refers to the transmission of sound primarily to the inner ear via “distortion” of the skull from the vibration of a bone oscillator. This “distortion” is transmitted from the skull to the bony labyrinth and causes compression and expansion of the membranous labyrinth thereby stimulating the structures responsible for transducing the auditory signal into a neuro-electric signal the brain will recognize.
- Sound energy travels following the presentation of a bone-conducted signal to the skull by three major pathways. (This is important to know because it is the basis for changes in bone conduction scores dependent upon the status of the outer and middle ear.)
 - Route #1: osseo-tympanic, the movement of the external ear canal walls produces sound energy that impinges on the TM
 - Route #2: inertial-movement of the ossicular chain results in stimulation of the cochlea
 - Route #3: distortional-the compression/expansion of the skull that results in movement of the basilar membrane and the outer and inner hair cells
- Carhart’s notch: A depression in the bone conduction score at 2000 Hz (a classic sign of otosclerosis). This phenomenon occurs due to a change in the inertial response of the middle ear system. Given that the resonant frequency of the ossicular chain is approximately 2000 Hz, fixation of the ossicular chain will result in a depression in the bone conduction score at that frequency.

- A similar depression to Carhart's notch can also be seen at other frequencies as a result of MEE, with a resulting improvement in bone conduction responses once the MEE has been resolved.
- If the outer ear is occluded, a low frequency bone conduction score can be artificially improved. This is known as the "occlusion effect". Recall the three pathways of bone conducted energy. Route #1 is via the movement of the outer ear canal. If the outer ear canal is occluded, the low frequency bone conducted energy is trapped in the outer ear canal and sent on to the cochlea, falsely improving the low frequency bone conduction scores. If the outer ear canal is open, the low frequency energy escapes.
- There are approximately 12,000 outer hair cells and 3,500 inner hair cells in each cochlea.
- Outer hair cells are stimulated by soft sounds while inner hair cells are stimulated by incoming sounds of 40 – 60 dB SPL.
- Damage to the outer hair cells typically results in hearing loss in the 40 – 60 dB HL range. Hearing loss greater than 60 dB involves both outer and inner hair cell damage.
- Ninety-five (95%) of afferent cochlear nerve fibers arise from inner hair cells and carry information to the brain. Efferent fibers terminate on the outer hair cells and carry information from the brain back to the cochlea.

AUDIOGRAM/SPEECH PERCEPTION/INTER-TEST CHECKS

- The Speech Detection Threshold (SDT) refers to the softest level at which the presence of speech is *detected* 50% of the time.
- The Speech Reception Threshold (SRT) refers to the softest level at which a speech signal (i.e., two-syllable highly redundant words known as Spondee) is *identified* 50% of the time.
- The Word Recognition Test utilizes phonetically balanced words and estimates one's ability to recognize speech at various sensation levels above the SRT. A "sensation level" (SL) refers to the total number of dB above a given pure-tone or speech threshold, at which the test stimuli is given. For example, a normal hearing individual, with an SRT of 10 dB HL, will likely achieve a score of 100% when word recognition testing is completed at 50 dB HL (aka 40 dB SL) re: his SRT.
- PEARL: The range of audibility between the softest and loudest speech sounds is approximately 30-35 dB.
- The SRT should be within 5-7 dB of the three-frequency average of the pure tone thresholds at 500, 1000, and 2000 Hz (i.e., the Pure Tone Average or PTA). A spread of 8-10 dB may occur in individuals with reduced word recognition abilities due to moderately severe or greater hearing loss.

- Differences in pure tone responses between tests should not vary by more than 5-10 dB (i.e., test-retest).
- PEARL: Word recognition abilities are known to be poor (25-50%) at lower sensation levels (i.e., 5-10 SL) with respect to the SRT. This is relevant when we obtain a word recognition score of 75% or greater at reduced sensation levels when testing an individual with a suspected non-organic hearing loss.

NATURE OF HEARING LOSS

- Conductive: Air conduction (AC) thresholds are below normal hearing levels and bone conduction thresholds are normal. Air Bone gap ≥ 15 dB.
- Sensorineural: Both AC and bone conduction (BC) scores are below normal hearing levels with air-bone gaps of ≤ 10 dB.
- Mixed: Both AC and BC thresholds are outside of normal limits and there is a difference between the air and bone conduction thresholds of ≥ 15 dB, or a hearing loss within an ear has both conductive and sensory components.
- PEARL: Every 10 dB increase in sound pressure level (SPL) is equivalent to a 10-fold increase in sound intensity, which generally equates to a doubling in loudness. A 20 dB increase in SPL is equivalent to 100-fold increase in sound intensity, which generally equates to 4x the loudness.

AUDIOMETRIC FINDINGS FOR DIFFERENT AGES/PATHOLOGIES

- Presbycusis is typically sensorineural and initially gently sloping; however, the slope becomes steeper with increased age (i.e., over 60), with the greatest depression seen at 8000 Hz.
- NIHL may be a sloping SNHL or a notched SNHL at 3000, 4000, or 6000 Hz.
- Hearing loss secondary to middle ear disease is often a flat conductive hearing loss (CHL) but can also slope slightly in the low and high frequency ranges.
- Perforations of the TM can result in no hearing loss or up to a moderate CHL dependent upon the size of the TM perforation and the volume of the middle ear space. The highest hearing loss with TM perforation and no ossicular discontinuity does not typically exceed 50 dB HL.
- A vestibular schwannoma may initially cause no hearing loss or a slowly progressive asymmetric high frequency SNHL. There can also be a low or mid-frequency SNHL in approximately 1/3 of individuals with vestibular schwannoma.

IMMITTANCE BATTERY

- An evaluation of hearing is not complete without immittance testing (i.e., the measurement of ear canal volume, tympanometry and acoustic reflexes).
- Tympanometry: Equivalent ear canal volumes, static compensated acoustic admittance, tympanometric peak pressure, and tympanometric width (also known as gradient).
- Acoustic reflex testing: Stapedius muscle reflexes.
- Tympanometry utilizes measurements of Tympanic Membrane (TM) “mobility” (or more accurately “admittance” and “impedance”) to infer middle ear function while the acoustic reflex test confirms the neural integrity of the VII and VIII nerve pathways in the low brainstem. Acoustic reflex testing can also help determine if there is a neural component to a SNHL.
 - Tympanometry and ear canal measurements are initiated by sealing the ear canal with a specially designed probe containing a manometer, a speaker, and a microphone.
 - The manometer increases the air pressure in the ear canal to +200daPa so that TM admittance of acoustic energy is negligible. While the speaker is simultaneously emitting a 226 Hz tone, a measurement of equivalent ear canal volume is made.
 - Ear canal volumes may range from 0.30-1.00 ml in children and from 0.65-1.75 ml in adults.
 - The air pressure is then decreased from +200 daPa to 0 daPa.
 - In a normally functioning ear, as the air pressure is decreasing, the TM admittance of acoustic energy is increasing, resulting in an upward moving tracing on the tympanometric graph.
 - Maximum displacement of the TM (or peak compensated static acoustic admittance) should occur when the air pressure in the outer ear canal is similar to that within the middle ear space (Normal range is approximately -100 daPa to +50 daPa).
 - The expression peak “compensated” static acoustic admittance indicates the ear canal admittance and volume have been subtracted from the overall admittance value obtained at the point of maximum TM displacement.
 - The pressure at which maximum displacement of the TM is obtained is considered the tympanometric pressure peak.
 - Once a peak is obtained, the air pressure is again increased from 0 daPa to -300 daPa (more negative values may be utilized during tests of ET function), once again decreasing TM admittance of acoustic energy, and resulting in a downward moving tracing on the tympanometric graph.

- Tympanometric width refers to the range of pressure at the approximate middle of the tympanometric tracing. A wider width and reduced admittance (i.e., mobility) are consistent with middle ear disorder.
- Tympanometry typically results in five commonly known tracings, developed by Liden and Jerger.

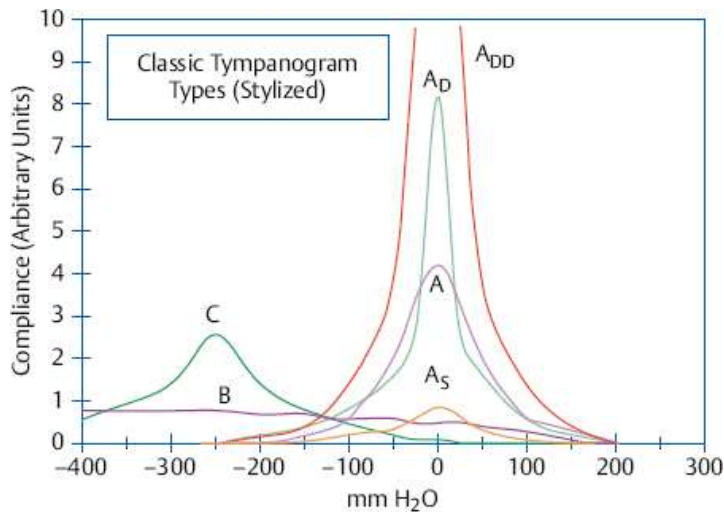


Figure 1. Common tympanogram types. Used with permission from <https://entokey.com/acoustic-immittance-assessment>.

- Acoustic reflex testing depends on normal TM mobility and middle ear pressure.
 - Utilizes the same probe as that used for tympanometry.
 - Is typically performed utilizing 500, 1000, and 2000 Hz tones.
 - Technique: A loud pure tone or pulsed tone is presented at 75-110 dB HL. The loud tone elicits the contraction of the stapedius muscle (i.e., the reflex), which in turn pulls the stapes and hence stiffens the ossicular chain, *decreasing TM admittance* (“compliance”), and the vibratory pattern received by the inner ear.
 - Normal acoustic reflex responses typically fall within 80-100 dB HL (or 0-85 dB SL re: pure tone thresholds at the frequencies tested).
 - A 3-neuron pathway that includes the ipsilateral VIIIN neurons, the ventral cochlear nuclei, and the VIIN motor nuclei primarily supports ipsilateral acoustic reflexes. Note: All nerve fibers from the cochlear nuclei will pass through the trapezoid body. Some of the nerve fibers will travel from the trapezoid body to the ipsilateral superior olivary complex before continuing to the VIIN motor nuclei, resulting in a 4-neuron pathway.
 - Contralateral acoustic reflexes are always dependent upon a 4-neuron pathway inclusive of the ipsilateral VIIIN neurons, the ipsilateral ventral cochlear nuclei, the ipsilateral superior olivary complex and the contralateral VIIN nuclei.
 - Elevated contralateral acoustic reflex responses (i.e., > 100 dB HL) are uncommon in normal hearing (-10 to 15 dB HL), slight hearing loss (16-25 dB HL), or mild

hearing loss (26-40 dB HL), and are expected in hearing losses at or greater than 45 dB HL.

SPECIAL TESTS

- A Stenger test is particularly useful in verifying a non-organic hearing loss. A signal is presented to the “better ear” at a level slightly above the volunteered threshold (i.e., the level at which the patient has chosen to respond versus the level at which the signal is just barely audible) while the same frequency signal is presented to the “poorer ear” at a level slightly below the volunteered threshold. If there is an actual hearing loss, the listener should respond because the signal is technically louder in the “better ear.” However, if the “poorer ear” is better than volunteered, the signal may be perceived as louder and the listener will not respond.
- Oto-acoustic emissions (OAE): Are a pre-neural by-product of the motile action of the outer hair cells as they respond to sound. They can be measured in the outer ear canal, provided there is normal outer hair cell function, middle ear space, and minimal debris in the outer ear canal. The presence of OAE’s infer normal sensory function within the cochlea.
- OAE testing has expanded our ability to evaluate the very young, confirm or disprove atypical pure tone configurations, and monitor for changes in hearing due to ototoxicity before there is a change in audiometric findings.
- There are two types of clinically used evoked OAE’s: Transient Evoked Otoacoustic Emissions (TEOAE’s) and Distortion Product Evoked Otoacoustic Emissions (DPOAE’s)
- TEOAE’s are stimulated by transient clicks (wideband) and typically present in individuals with a hearing loss no greater than 30 dB HL. Present TEOAEs in an individual with SNHL may herald either a retro-cochlear pathology or a non-organic hearing loss.
- DPOAE’s are a bi-product of the simultaneous delivery of 2 strategically selected pure-tones to the cochlea. The first pure tone is known as “ f_1 ” and the second is known as “ f_2 ” with “ f_1 ” being a lower frequency. The ratio of “ f_1 ” to “ f_2 ” is 1.20. The “distortion product” that results from their simultaneous presentation typically occurs within the frequency range of $2f_1-f_2$.
- Of note: The “distortion product” is not the value that best correlates with estimated responses on the audiogram: “ f_2 ” is. A “distortion product” can actually occur within an area of the cochlea that has damaged hair cells, as it is the result of basilar membrane movement due to the interaction of two other entities, and not a directly elicited response from that region of the cochlea.
- DPOAE’s may be used to look at outer hair cell function with hearing loss up to 45 – 55 dB HL.

- The presence of a pressure equalization tube in the TM reduces the chances of obtaining TEOAEs by 50%.
- Auditory brainstem response (ABR) tests retro-cochlear function and is the composite result of electrophysiological responses (i.e., a change in resting potentials in response to an auditory stimulus) from several sites along the auditory pathway. It is obtained by placing electrodes behind the mastoid and on the high forehead or vertex. The ABR occurs within the first 10 milliseconds following the stimulus presentation.
- The evoked potentials may be greater in voltage at some points along the auditory pathway (i.e., “peaks”) as compared to others (“troughs”). These responses are very repeatable in a normal hearing person and can be represented graphically by a series of waveforms.
- Although there is the potential for 7 peaks within the auditory brainstem response, waves I-V are typically the most prominent, with waves I, III, and V primarily used in the analyses of the ABR.
- Two primary indices utilized to describe or evaluate ABR waveforms are absolute and inter-peak latencies (i.e., time of occurrence of each waveform and the intervals between each waveform in msec.) and amplitude (i.e., total response in microvolts).
- Of equal importance are the inter-aural differences between wave V absolute latencies (a normal difference would be 0.3-0.4 msec) and the shift in each wave V absolute latency at an increased click rate (a normal shift = 0.1 msec increase in wave V absolute latency per each 10 point increase in stimulus rate).
- With decreases in stimulus intensity, the amplitudes of waveforms will decrease and the latencies will increase. When searching for a threshold response, early waveforms will no longer be identifiable. The lowest intensity that Wave V can be identified is considered the eHL threshold.
- CHL and SNL can either influence the time of occurrence of the ABR waveforms or result in their total absence (e.g., CHL results in the prolongation of all waveform latencies and/or a reduction in amplitudes while a significant high frequency SNHL can result in the absence of wave I).
- The dB values utilized when reporting ABR responses do not have a one-to-one correlation with an audiogram. A “0” dB ABR stimulus correlates with 0-25 dB HL. Thus, 0 dB nHL for ABR testing is representative of an average response from a pool of normal listeners for a given stimulus. This phenomenon is due in part to the difference in stimuli utilized to evoke the ABR.
- Electrocochleography (ECOG) refers to the measurement of neuroelectric events that are produced by the cochlear structures in response to acoustic stimulation. The response includes the cochlear microphonic, the summing potential (SP), a DC current, and the whole-nerve action potential (AP), an AC current by the auditory nerve. In Meniere’s disease, the elasticity of the basilar membrane is believed to be affected resulting in a large SP/AP amplitude ratio.

HEALTH CONDITIONS AND HEARING LOSS

- Cardiovascular disease: low frequency SNHL may be an indicator.
- Chronic kidney disease: results in a higher prevalence of hearing loss.
- Diabetes: The 1999-2004 National Health and Nutrition Examination suggested a high occurrence of hearing loss among diabetic participants; however, more than 50% of participants also had high cholesterol, and/or hypertension, and 20% had coronary artery disease.
- Cognitive function: Unaided hearing loss has been associated with a greater rate of decline (i.e., 30-40%) in cognitive function in older adults with hearing loss as compared to older adults with normal hearing.

HEARING AIDS

- Hearing aids and assistive listening device selections are individualized to patient's communication and lifestyle needs and are assessed during a hearing aid evaluation.
- Common considerations include: degree and nature of hearing loss, dynamic range, speech-in-noise and/or localization abilities, complexity of listening situations, hearing handicap, dexterity, phone use, and concomitant medical conditions.

TERMINOLOGY

- Dynamic range: Range of hearing between a person's hearing threshold and uncomfortable loudness/loudness discomfort level.
- Gain: difference in sound pressure between the amount of sound coming in to the hearing aid and the resulting sound as it leaves the hearing aid receiver (i.e., output minus input).
- Output: the maximum power output (MPO) or saturation sound pressure level (SSPL) of the hearing aid (i.e., the maximum sound level that the hearing aid can produce).
- Frequency Response Curve: the range of frequencies in which sound is amplified.
- Compression: variance in gain as input level changes.
 - Kneepoint: Level of sound that result in a reduction in the gain of a signal, relative to an increase in input.
 - Compression ratio: Amount of change in input relative to the resulting change in output.
 - Attack and release: Amount of time it takes the hearing aid circuit to respond to changes in input.

- Linear compression: Gain stays the same as input changes (1:1 relationship) until maximum output of hearing aid is reached.
- Output limiting: Peak clipping when the hearing aid reaches limits of amplification.
- Input compression: Hearing aid compresses a signal before it reaches the volume control. Changes in volume control affect both gain and output.
- Output compression: Hearing aid compresses a signal after it reaches the volume control. Changes in volume control affect gain not output.
- Wide Dynamic Range Compression (WDRC): Compression activates throughout the dynamic range, typically allows greatest gain for soft sounds and less gain for loud sounds.
- Acoustic feedback: Oscillations resulting when sound produced by the hearing aid receiver reaches the microphone and is re-amplified. Resulting sound is a high-pitched squeal.
- Adaptive feedback suppression: Hearing aid detects feedback and applies an algorithm to reduce it. Methods used include notch filters, phase cancellation, or a combination thereof.
- Vent: Opening or bore made in an earmold or custom hearing aid to allow the passage of sound and/or air into an ear canal which is otherwise blocked by the device. Venting offers acoustic changes to the hearing aid response and can offer pressure release or aeration to the ear. A shorter vent with large diameter is most effective at reducing low frequency output.

HEARING AID COMPONENTS/STYLES

- Traditional amplification includes component parts of a microphone, digital filters, receiver and power source.
- Analog hearing aids have been replaced by digital technology.
- Earmolds: Custom earmolds are made from an impression of the hearing aid user's ear and typically result in a better fit. Non-custom molds (eg domes) can be used with RITE/RIC and slim- or thin-tube hearing aids.
- Behind-the-ear (BTE) hearing aid – all components are housed in the hearing aid that sits behind the ear and is coupled via a tube to a custom earmold. BTE's hearing aids are commonly used for those with severe-to-profound hearing loss, excessive cerumen production, ear drainage, and poor vision or dexterity. BTE's are also used with children and allow coupling to Frequency Modulation (FM) listening systems.
- Slim- or Thin-Tube – A thin tube can be connected to a BTE hearing aid for a mild or moderate hearing loss with normal low frequency hearing.
- Receiver-in-the-ear (RITE) aka Receiver in the canal (RIC) – the microphone, amplifier and power supply are housed in the hearing aid which generally sits on top

of and slightly behind the ear and is coupled to a receiver inside the ear canal. This style provides an “open” fit with the receiver covered by a non-custom earmold or dome. For more severe hearing loss, the receiver can be covered with an occluding dome or can be encased in a custom earmold to prevent feedback. RITE and RIC hearing aids can be fit from mild to severe hearing loss including normal to steeply sloping hearing loss. RITE/RIC hearing aids are generally covered by the superior portion of the pinna and are most preferred for improved directional hearing as well as cosmetic appeal.

- In-the-Ear (ITE) – all components are housed into a custom fit hearing aid that fills the concha and helix portions of the ear. This style is most appropriate for those with a moderate to severe hearing loss who desire a single piece. Those with limited fine motor skills find the ITE easier to place.
- In-the-Canal (ITC) - all components are housed in a custom fit hearing aid that fills the concha and fits up to a severe hearing loss.
- Completely-in-the-canal (CIC) – all components are housed into a custom fit hearing aid that fits deeply in the canal placing the receiver closer to the eardrum. This hearing aid is for high frequency hearing loss and does not provide adequate gain for low frequency loss. CIC and mini CIC hearing aids are preferred by some for cosmetic advantages.
- Bone conduction - BTE hearing aids can be modified to power a bone oscillator for severe CHL. Developments in osseointegrated aka bone-anchored hearing aids (BAHA) have nearly replaced the need for or use of traditional bone conduction devices.
- Custom hearing aids (e.g., CIC, ITC, ITE) have a greater chance of feedback due to the short distance between the receiver and microphone. Amplified sound leaking from the ear has a direct path back into the microphone of the hearing aid. BTE and RITE hearing aids can also have feedback with a poorly fit earmold.
- When fit binaurally, hearing aids offer advantages such as: a) improved localization, b) a 2-3 dB signal to noise ratio improvement due to elimination of the head shadow effect and binaural squelch, and c) enhanced hearing due to summation between ears.

CROS/BICROS

- A wireless contralateral routing of signal (CROS) system utilizes a microphone and transmitter behind the poorer ear routing sound to a receiver on the better, normal hearing, ear.
- CROS (Contralateral Routing of Signal) hearing aid is used for unilateral SNHL hearing loss. Sound is transmitted from the poor ear to the normal hearing ear.
- A Bi-CROS hearing system is utilized when hearing loss also exists in the better ear. In this case, the receiving instrument also functions as a hearing aid to amplify sound to the better ear.

OSSEOINTEGRATED DEVICES (OID)/ AKA BONE ANCHORED HEARING AIDS (BAHA)

- These devices provide bone conducted sound via direct vibration coupled to a titanium fixture or magnetic coupling that has been surgically implanted into the skull. They are appropriate for CHL (e.g., microtia, atresia, stenosis, chronic drainage) and mixed hearing loss with bone conduction scores no worse than a moderate severity level. For patients under the age of five whom do not yet have the appropriate bone thickness, the bone oscillator portion of the device can be coupled to a soft headband.
- OID/BAHA devices can be effective for single-sided deafness (SSD) by which the sound from the poorer ear is transmitted through the skull to the better cochlea. This is most successful in those with normal hearing in the “good ear”.

MIDDLE EAR IMPLANTABLE HEARING AIDS

- Maxum is a partially implantable hearing device that consists of a rare-earth magnet implanted on the middle ear bones and works with a canal style processor that uses electromagnetic energy to vibrate the implant. Working without a speaker, the Maxum has less distortion, reduces feedback and minimizes occlusion. The ideal candidate is an adult with moderate to severe sensorineural hearing loss
- The Esteem hearing aid is a fully implantable device. The device has 3 components, a sensor that picks up vibrations from the incus, a driver that delivers increased mechanical energy to the stapes, and the sound processor that processes and amplifies the acoustic signal. The Esteem fits adults with moderate to severe SNHL and requires normal TM, middle ear, and Eustachian tube function. Additionally, the middle ear space must be adequate in size to house the implant. Cosmetic and lifestyle advantages (e.g., swimming, showering) are appealing; however, surgery is required every few years to change the battery.

COCHLEAR IMPLANTS (CI)

- The CI processor is an external device that works with the implant. Components include a microphone to pick up sound, a sound processor that converts sound to an electric signal that is sent to a headpiece to stimulate the internal implant.
- CI processors are available in multiple styles including BTE processors, a smaller off the ear style processor that is fully contained in the headpiece, and a body worn waterproof device. US FDA approved CI's are currently available from Advanced Bionics, Cochlear and MedEl.

CANDIDACY

- A 3 – 6 month hearing aid trial is recommended prior to implantation with exceptions for special circumstances (e.g., meningitis due to cochlear ossification).
- General candidacy for adults (18+ years): moderate to profound SNHL in both ears; limited benefit from appropriately fit binaural amplification defined by scores of $\leq 50\%$ sentence recognition in the ear to be implanted and $\leq 60\%$ in better ear or binaurally. Medicare coverage currently has a stricter definition of candidacy, $<40\%$ in best-aided condition.
- Candidacy for children (2 – 17 years): severe to profound SNHL bilaterally, limited benefit from binaural amplification with appropriately fit hearing aids.
- Candidacy for children (12 -24 mos.): profound SNHL, limited benefit from binaural amplification trial including failure to reach auditory developmental milestones.
- Off label use of implants is increasingly considered as technology improves (eg <12 months of age, unilateral hearing loss).
- The Minimal Speech Test Battery (MSTB) is the recommended test battery, for adults, by all three US FDA approved CI companies for use in cochlear implant candidacy and post-implant testing. The MSTB consists of AZ Bio sentences in quiet and in noise, CNC monosyllabic words in quiet, and BKB-SIN sentences in noise test. A Pediatric AZ-Bio test is also available.
- CI's can be implanted in one or both ears (bilateral) or work in conjunction with a hearing aid in the opposite ear (bimodal). Hybrid and Electrical Acoustic Stimulation are combined cochlear implant and hearing aid solutions built into a single processor. These devices allow acoustic energy to be used for the better hearing in the low frequencies and electrical stimulation for the severe-to-profound hearing loss in the mid and high frequencies.
- Hybrid CI's are available for adults (18 years +) who have aidable hearing in the low frequencies (e.g., through 500 Hz) and a severe-to-profound hearing loss in the mid to high frequencies. General candidacy considers recognition of CNC words between 10 and 50% in the poor ear and $<80\%$ in the better ear, using appropriately fit hearing aids.
- Electric Acoustic Stimulation CI's are available for adults (18 years +) with normal to moderate SNHL hearing loss in the low frequencies sloping to severe-to-profound hearing loss in the high frequencies with CNC word scores of $\leq 60\%$ in the ear to be implanted.

ASSISTIVE LISTENING DEVICES (ALD's)

- ALD's can be used with all forms of amplification or with special receivers for those who do not wear hearing aids.

- A variety of frequency modulated (FM) and infrared devices are available to work with or without amplification to improve the signal to noise (SNR) ratio in difficult listening situations (e.g., classrooms, TV). These are most commonly used with kids in classrooms.
- Personal FM systems wirelessly transmit sound via a receiver attached to a BTE hearing aid or cochlear implant, or through a neckworn hearing loop that connects to a custom hearing aid via a telecoil.
- SNR ratios are improved with FM systems by separating the microphone from the receiver. The speaker (e.g., the teacher) wears the microphone and the listener wears the receiver (e.g., hearing aid, ear level receiver, and headset).
- Childhood mild hearing loss, particularly transient or unilateral, may be treated with personal or classroom FM systems. FM systems are wire-free, portable, and are not obstructed by physical barriers therefore can be used indoors and outdoors. Personal FM systems have a distance of about 50 feet (up to max of 300 feet). A disadvantage of FM systems is interference from other signals using radio waves in the same frequency range (e.g., radios, walkie talkies).
- Permanent mild hearing loss may be better treated with hearing aids. Classroom FM systems (aka Classroom Audio Distribution Systems) provide an improvement in the signal to noise ratio for everyone in the classroom. These systems assist students in hearing above typical classroom noise (e.g., shuffling papers, noise from fans or ventilation systems, moving of chairs, students talking) and are helpful for those with mild or transient hearing loss and auditory processing disorders.
- FM signals are wireless and transmitted across a large area such as a classroom, living room, auditorium or church.
- Infrared assistive listening devices are wire-free and operate on line of site. They have excellent transmission of music and speech (e.g., TV listening). Disadvantages: can only be used inside, AC powered so limited portability, and signal easily disrupted by objects within the line of site.
- Bluetooth devices transmit directly to the receiver via wireless radio waves. A variety of Bluetooth devices connect to BTE and RITE hearing aids and CI's via a streaming device. Bluetooth transmission is limited to 40 – 60 feet.
- Commonplace Bluetooth devices stream sound between a sound source (e.g., cell phone, TV, remote microphone) and the hearing aid. The interfacing device (ie streamer) receives sound from the sound source and transmits that sound to the hearing aid.
- Advanced hearing aid technology now allows direct Bluetooth connection between the hearing aids and the signal source (e.g., cell phone).
- Hearing Loops are special sound systems placed around a perimeter of a room or large public area and transmits magnetic energy to telecoil-equipped hearing aids, cochlear implants or neck loops with earphones.

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Chapter 18

HEARING LOSS: CONDUCTIVE AND SENSORINEURAL

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- Congenital hearing loss is the most common sensory defect occurring in 1 in 1,000-2,000 live births.
 - Early identification and intervention is key.
 - 70% of cases are nonsyndromic.
 - 30% of cases are related a syndrome.
 - 75-80% of cases are due to autosomal recessive genes.
 - 18-20% are due to autosomal dominant genes.
 - 1-3% are due to X-linked or chromosomal disorders.
 - Environmental factors include but are not limited to: rubella, cytomegalovirus, kernicterus, syphilis, herpes simplex virus, and hypothyroidism.
 - Nonsyndromic congenital hearing loss that accounts for 70% of cases is likely linked to over 100 genes. Connexin 26 mutations are the most common mutations for nonsyndromic congenital SNHL.
- Select Autosomal Dominant Syndromes.
 - **Branchio-Oto-Renal Syndrome** – children have ear pits/tags, cervical fistula and renal involvement. 75% of patients have hearing loss with 30% being conductive, 20% SNHL, and 50% mixed.
 - **Osteogenesis Imperfecta** – presents with varying degrees of bone fragility, blue sclera, conductive, mixed, or SNHL.
 - **Stickler Syndrome** – characterized by cleft palate, micrognathia, myopia, retinal detachments with a marfanoid habitus.

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- **Treacher Collins** – constellation of facial malformations including hypoplasia of the mandible and maxilla, congenital aural atresia, microtia, cleft palate and dental malocclusion. CHL is present approximately 30% of the time but SNHL can also be present.
- **Waardenburg Syndrome** – most common form of autosomal dominant congenital hearing loss. Variability in presentation there can be unilateral or bilateral SNHL.
- Select Autosomal Recessive Syndromes.
 - **Jervell and Lange – Nielsen Syndrome** – profound SNHL and cardiac dysrhythmias. Mutation affects a potassium channel gene that effects conduction within the heart. Children with early hearing loss should get an EKG for evaluation.
 - **Pendred Syndrome** – profound SNHL and thyroid goiter. Hearing loss can be progressive in approximately 15% of patients. Mutation in PDS gene coding for pendrin protein.
 - **Usher Syndrome** – most common type AR syndromic hearing loss and affects almost one half of deaf and blind in the United States. Characterized by SNHL and retinitis pigmentosa. 3 different subtypes of the syndrome. Patients with hearing loss should undergo formal ophthalmologic examination.
- **Alport Syndrome** – X-linked disorder where the collagen of the basement membrane of the kidneys and inner ear effected. Patients have progressive renal decline and progressive SNHL.

SENSORINEURAL HEARING LOSS

- Sensorineural hearing loss is exceptionally common and effects patients of ages. It can range from being undetectable to a severe impairment affecting nearly all aspects of life.
- Between 30-35% of patients over the age 65 have hearing loss significant enough to necessitate a hearing aid. That number rises to 40% by age 75.
- SNHL results from damage to hair cells, structures within the inner ear, or the eighth cranial nerve.
- Causes for SNHL can include:
 - Noise Exposure
 - Meningitis
 - Cochlear otosclerosis
 - Aging
 - Meniere's Syndrome
 - Temporal bone fractures

- Pathogen Infections
- Medications
- Idiopathic
- Autoimmune
- Retrocochlear lesions i.e., tumors
- Ototoxic medications can cause sensorineural hearing loss:
 - Aminoglycoside antibiotics
 - Acetaminophen
 - Chemotherapeutic agents notably cisplatin
 - Salicylates
 - Quinine and synthetic analogs of quinine
- **Presbycusis** – age associated hearing loss in adults. Most common cause for hearing in adults. Typically presents as symmetric, high frequency hearing loss that progresses to involve lower frequencies. Patients experience a decline in the clarity of their hearing. As neuronal loss progresses patients will have progressive loss in speech discrimination and yet may retain relatively good pure tone average. In seeing patients with hearing loss, the word recognition is just as important as the pure tone average. Recent studies have shown associations with hearing loss social isolation and poorer cognitive function in the elderly.
- **Noise induced hearing loss** – preventable form of SNHL and the second most common form of SNHL. Approximately 20 million Americans are exposed to hazardous noise. Avoiding loud noise exposure and regular use of hearing protection can help to prevent or limit noise exposure. OSHA regulations require hearing protection at 85 dB for 8 hours, 100 dB for 2 hours and 115 dB for 15 minutes. Temporary threshold shift is a temporary SNHL that resolves within 24 hours following exposure to loud noises.
- **Sudden Sensorineural hearing loss** – loss of over 35 dB in at least 3 adjacent frequencies over less than 3 days. Overall incidence is approximately 1 in 5,000. Worse prognosis in the elderly, total hearing loss, longer duration of deafness, down-sloping audiogram, delayed treatment and in those patients with associated vestibular symptoms. Tinnitus is common and is seen in 80-100% of patients. Typically idiopathic can be autoimmune, viral, or vascular in etiology or represent first episode of Meniere's syndrome. Blood tests are rarely obtained but can include CBC, ESR, FTA-ABs, coagulation and thyroid studies. Key point is to obtain and MR to exclude retrocochlear lesion which is present in 1 in 20 of these patients. In idiopathic cases, patients are typically treated with high dose oral steroids (typically 1 mg/kg for 10-20 days) initially with transtympanic steroids for salvage or initially for patients that cannot tolerate high dose oral steroids. Hyperbaric oxygen has not shown reliable rates of improvement

compared to natural history. AAO-HNS guidelines indicate that it can be offered as adjuvant therapy within 3 months of onset.

- **Autoimmune inner ear disease** – Typically presents as progressive and ultimately bilateral SNHL. Often will be asymmetric SNHL at a given point of time. Presumed to be due to immunological attack on the inner ear or an associated systemic autoimmune disorder. Unknown pathophysiology with 15-30% of patients having systemic autoimmune disease. History is very important in making the diagnosis. Made by serial audiograms demonstrating rapidly progressive usually bilateral hearing loss. Heat shock protein 70 has been shown to be a helpful marker. Treatment involves corticosteroids and for some patients steroid-sparing immunosuppressants. Typical causes include Polyarteritis nodosa, Wegener granulomatosis, SLE, Cogan syndrome (interstitial keratitis, vestibular dysfunction and SNHL),
- **Meningitis** – Meningitis with associated labyrinthitis ossificans is overall a relatively rare cause of SNHL. This is due to wide scale pneumococcal vaccination helping to prevent the development of meningitis and the resulting labyrinthitis ossificans. Typically, ossification occurs basally near the round window most likely via the cochlear aqueduct. High suspicion and early MR and CT are key. MR identifies early fibrosis and demonstrates fluid patency whereas CT demonstrates neo-ossification. In patients with SNHL hearing loss, that meet criteria early implantation should be considered when fibrosis is demonstrated.
- **Retrocochlear** – Though overall rare retrocochlear lesions are an important diagnostic consideration. The two most common lesions are acoustic neuromas (vestibular schwannomas) and meningioma. Patients with retrocochlear lesions characteristically will have an asymmetric SNHL often with often a surprisingly poor speech discrimination score on that side. Often patients will seek evaluation evaluation stating they are having a hard time using a cellular phone on that side. Patients with asymmetric SNHL, SSNHL, unilateral tinnitus or other otologic symptom warrant an MR to exclude a retrocochlear lesion. If they cannot undergo an MR then CT with contrast and ABR (if their hearing permits) are another diagnostic consideration.
- **Auditory neuropathy** – Spectrum disorder that abnormally activates the auditory system. Lesion site can range from the inner hair cells to the cochlear nerve itself. OAEs will be present and ABR will be abnormal to absent. Audiologic performance and speech perception abilities can be variable in this population and can range from normal to profound.
- **Treatment** – Treatment for SNHL can range from preventing it in the case of noise induced hearing loss to utilization of hearing aids, middle ear implants, and cochlear implantation.

CONDUCTIVE HEARING LOSS

- Conductive hearing loss occurs when there is an issue transmitting sound waves from the environment to the inner ear. The issue can arise at the outer ear, within the EAC, tympanic membrane, ossicles or within the middle ear. This can occur in isolation or occur in conjunction with SNHL resulting in a mixed hearing loss.
- Differential diagnosis for CHL:
 - Cerumen obstruction
 - EAC lesion
 - Otitis externa
 - Otitis media
 - TM perforation
 - Otosclerosis
 - Cholesteatoma
 - Hemotympanum
 - Ossicular discontinuity
 - Third Window Effects
 - Middle ear lesion
- **Cerumen obstruction** – can be a cause for CHL or MHL if there is a preexisting SNHL. Examination will demonstrate cerumen completely filling the EAC obstructing sound waves from reaching the tympanic membrane. Removal of the cerumen results in resolution of the CHL.
- **EAC Lesion** – EAC lesions most commonly seen are exostoses and osteomas that rarely can cause CHL.
- **Otitis externa** – In approximately 30% of cases patients can develop CHL due to stenosis of the EAC. Resolves with appropriate treatment and aural toilet. In patients that are immunocompromised esp. diabetics and patients that have worsening otalgia, develop cranial neuropathies, and/or fail to improve with usual treatment consideration should be made for a diagnosis of malignant otitis externa.
- **Otitis media** – Acute otitis media (AOM), otitis media with effusion (OME), and chronic otitis media (COM) all can result in CHL. The reason for CHL for each varies. For AOM acute inflammation and the development of purulence within the middle ear. OME is defined by the presence of non-infected effusion which can cause CHL. COM can cause CHL via tympanic membrane perforation, adhesive OM with TM retraction, ossicular erosion, and cholesteatoma.
- **Tympanic Membrane perforation** – Tympanic membrane perforation can be caused by several different injuries. These can include cotton – tipped applicator and other foreign body, slap to the ear, pressure from diving into water, sudden loud noises, slag, barotrauma and otitis media. Degree of CHL hearing loss

varies on the size and the location of the perforation. The larger the perforation the greater the hearing loss and posterior perforations generally tend to have greater hearing loss.

- **Cholesteatoma** – Lesions of keratinizing stratified squamous epithelium that contain keratin. Most often occur within the middle ear and mastoid but can involve any part of the temporal bone that has pneumatization or intracranial space. Can be congenital, primary acquired, or secondary acquired. Early stages of disease can be asymptomatic with the most common presenting symptom being otorrhea. Progressive CHL is often present during the natural history of the disease. Of note, it is possible for the cholesteatoma to erode the ossicles and for the patient to effectively hear through the cholesteatoma. Primary objective in ears with cholesteatoma is provide a safe, dry, and disease free ear with the best hearing outcome as a secondary objective.
- **Otosclerosis**
 - Disease characterized by abnormal bone remodeling of the otic capsule. Foci of endochondral bone are replaced by hypercellular bone which than can develop into sclerotic bone. Approximately 50% of patients will have a family history and up to 70% will have bilateral disease. Autosomal dominant with variable penetrance.
 - Can be due to fixation of the stapes footplate with the development of CHL or cochlear involvement with SNHL development.
 - It is the most common cause of progressive CHL in adults. Mean age of diagnosis is between 20 and 40 years of age and is twice as common in women as men.
 - Most common site of stapes footplate fixation is the fissula ante fenestram (anterior to the oval window). Clinically, dilation of the vessels on the promontory can be seen (Schwartz's sign). Tuning fork shows negative Rinne at 250 Hz early in disease, and then worsening to other frequencies. A negative Rinne at 250 indicates 15 dB loss, at 512 indicates 25-30 dB loss and at 1,024 Hz of at least 35 dB hearing loss. Audiogram shows flat or "cookie bite" with excellent discrimination. Tympanogram may show As configuration. CT may reveal "double ring" sign that represents cochlear demineralization. Stapedial reflexes should be absent. Histologically, can see "blue mantles of Manasse" on H&E stain that represents areas of ground substance deposition.
 - Most common presentation is a normal dry ear with little otologic history with conductive hearing loss as the presenting symptom. A significant number of patients will demonstrate paracusis of Willis that effected patients hear better in noise. Indications for surgery include a CHL over 25 dB in speech frequencies. Contraindications include only hearing ear, TM perforation, middle ear disease, and vestibular symptoms. Options to discuss with patients include observation, amplification and surgery. In experienced hands closure of ABG less than 10 dB

90-95%. Risks of surgery include failure to improve hearing, loss of hearing (less than 1%), tinnitus, vestibular dysfunction, perilymphatic fistula, facial nerve injury, dysgeusia, TM perforation, and late surgery failure.

- Surgery: The risks, benefits, and expectations of each treatment option need to be discussed in detail with the patient. The patients' options include observation, amplification, stapes surgery and BAHA placement. Patients do not need to have an amplification trial prior to proceeding with stapes surgery. They do need to understand completely and consent that there is a very rare risk of complete hearing loss even with a perfect surgery.
- Reparative granuloma presents as progressive SNHL with lower discrimination scores (granulation tissue on the oval window area and exam shows reddish discoloration behind TM). This is very rare and associated with gelfoam use. Surgery is needed immediately.
- Fluctuating hearing loss after surgery may indicate perilymph fistula (requires exploration). Persistent vertigo after surgery may indicate long prosthesis.
- Failure of stapedectomy is most commonly a result of prosthesis displacement
- **Hemotympanum** – Most commonly secondary to trauma, diagnosed on microscopic otoscopy. Results in a conductive hearing loss that will clear over 6 weeks. Obtain audio after clearance and breakdown of blood to ensure resolution of hearing loss and may identify ossicular discontinuity.
- **Ossicular discontinuity** – Typically occurs after trauma. Presents as CHL that is present after resolution of hemotympanum. Most common discontinuity is incudostapedial joint disarticulation followed by incus dislocation and stapes crura fracture. Options include observation, hearing aid, bone conducting hearing aid, and middle ear exploration with ossiculoplasty.
- **Third window effects** – Presence of an abnormal window in the otic capsule such as superior semicircular canal dehiscence, fenestration, or enlarged vestibular aqueduct can cause CHL. Loss of acoustic energy through such a dehiscence causes an abnormal shunting through the vestibular system causing hearing and balance issues.
- **Middle ear lesion** – Overall a rare cause for CHL but an important diagnostic consideration. Patients with these types of lesions typically have isolated conductive hearing loss unless there is labyrinthine involvement. These lesions include:
 - Paraganglioma – arise from chief cells that are of neural crest origin. Key pathology – cluster of nonchromaffin-staining cells known as zellballen. Tympanicum most common middle ear neoplasm arising from Jacobson's (IX) and Arnold's nerve (X). Jugulare are the most common jugular foramen lesion and originate from paraganglion cells in the adventitia of the jugular bulb. Due to location of jugular bulb, a growing lesion can involve the middle ear causing

CHL. Vagal lesions originate along the path of the vagus nerve and cause CHL via similar means to jugulare lesions.

- Primary middle ear adenomas – another rare cause for CHL.
- Unilateral effusions – Though not a true lesion of the middle ear the presence of a unilateral middle ear effusion in an adult should raise ones clinical suspicion for a potentially sinister cause and start further investigation. This could be the result of nasopharyngeal lesion causing Eustachian Tube dysfunction and cause the unilateral effusion. Adult patients with a unilateral effusion should undergo endoscopic evaluation of their NP to evaluate for a lesion. Another important consideration is the potential for a skull base defect and a resulting unilateral CSF effusion.

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Chapter 19

SIGN ACQUISITION AND DEVELOPMENT BY HEARING CHILDREN WITH AUTISM SPECTRUM DISORDERS

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INTRODUCTION

Childhood autism, once viewed as a rare clinical disorder, has come to be recognised as a major form of developmental disability. This change in perspective rests largely on the rapidly increasing estimates of the incidence of children on the Autism Spectrum (ASD) or with other closely related syndromes. Sixty years ago, childhood ASD was depicted as very uncommon, occurring in only one or two children per 10,000. By 1996, the estimated incidence had climbed to about one in every 500 children (Bristol et al., 1996). More recently, an estimated incidence of one in every 59 children was reported¹. This marked increase in the number of children diagnosed with ASD has sparked alarm in many quarters and led to ASD being recognized as a major public health priority (Bonnet-Brilhault, 2017). This chapter reviews research into the use of sign to support spoken language in children with ASD (that is, using some form of simultaneous communication or key word signing system), referencing also some recent studies of deaf children on the Autism Spectrum, a topic explored in more detail in Chapter 7.

What factors might be behind this apparent rapid increase in the incidence of childhood ASD? An important factor is that our understanding of what constitutes autism has changed. In the initial description of the syndrome of childhood autism by Leo Kanner (1943), these children were depicted as self-absorbed and as having serious behavioural, social, and

¹ (<https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm> Accessed 10th July 2018).

communicative difficulties. Early understandings of autism grew out of the childhood schizophrenia literature, often with psychoanalytic interpretations. This depiction prevailed until recent years, although differing perspectives were occasionally presented. Hans Asperger, a contemporary of Kanner, described autistic children somewhat differently. Although the children he worked with were portrayed as having many of the same behavioural characteristics first described by Kanner, some of the youngsters with whom Asperger worked demonstrated good formal language skills and scored quite highly on measures of intellectual abilities. It is this more inclusive view of childhood autism, with a much wider range of abilities represented, that has become the more generally accepted view of autism (Frith, 2008; Silberman, 2015). This diversity of abilities is captured in the now widely used term Autism Spectrum disorder (ASD).

The expansion of diagnostic criteria probably accounts for much of the apparent increase in the incidence of ASD (Gernsbacher, Dawson & Goldsmith, 2005), along with diagnostic substitution. For example, many individuals who had previously been identified as intellectually disabled were subsequently diagnosed as autistic (Croen et al., 2002). A growing awareness of the characteristics of childhood ASD by both parents and professionals has probably also led to more children being identified. Finally, the increasing availability of programmes for these children may have sparked more parents to push for a formal diagnosis in order to qualify for support. Other factors, such as parents having children at older ages, medications used during pregnancy, and environmental pollution, may also be contributing to an increased incidence. While the above factors probably account for most of the apparent increase in the incidence of ASD, it should be acknowledged that there is an ongoing debate as to whether this increase is real.

COMMUNICATION TRAINING INTERVENTIONS

In the two decades following Kanner's initial account of the characteristics of children with ASD in 1943, very little progress was made in developing effective therapeutic interventions for these children. An area of particular difficulty, and one often resistant to change, was their atypical communication. Difficulties included delayed spoken language development, particularly in the area of pragmatics; the immediate or delayed repetition of others' utterances (or echolalia), and the absence of speech. These problems in communication were of special concern to therapists because the prognosis for those children who failed to acquire useful speech by the age of 5 or 6 years was very bleak (Eisenberg, 1956), with lifelong institutionalisation the likely outcome (Lotter, 1974). For those children who did acquire useful speech, much more positive long-term outcomes were reported (Howlin et al., 2004; Lord & Bailey, 2002).

Behaviour Modification Programmes

An important innovation in the fostering of language or communication skills in children with ASD was the introduction of behavioural techniques. Now generally referred to as Applied Behavioural Analysis (ABA), the approaches have been criticised on several

grounds, including the use of negative reinforcement and the emphasis on control (see Gruson Wood, 2016), although there is a continuum of implementation (Kates-McElrath & Axelrod, 2006). The approach originated in the 1960s with the research of Ivar Lovaas and his associates. They showed that by systematic application of rewards contingent on the children's behaviour, many children with ASD were able to make substantial progress in spoken language (Lovaas, 1977; 1987; Lovaas et al., 1973). However, this progress was not shared equally amongst the children involved. Whereas those children who had some useful speech or who repeated others' speech (that is, they were echolalic) often made considerable gains, others did not fare as well. In particular, those children who were mute or minimally verbal at the time they entered Lovaas' programme typically made little progress in acquiring communication skills (1977). Such minimally verbal children, moreover, constituted a significant proportion of the children diagnosed with ASD. Historically, those children who had no or little speech were estimated to account for between one-third and one-half of children with ASD (Lord & Paul, 1997; Mesibov, Adams & Klinger, 1997; Peeters & Gillberg, 1999). With the expansion of the diagnostic criteria for ASD and the introduction of early intervention programmes in recent years, the proportion of children with little or no speech skills has decreased. More recent estimates of those children diagnosed with ASD who fail to acquire useful spoken language skills range from 20 to 30 percent (Kim & Lord, 2014; Tager-Flusberg & Kasari, 2013; Wodka, Mathy & Kalb, 2013).

Sign Communication Programmes

A second important innovation in language and communication training for children with ASD occurred in the 1970s with the introduction of sign communication programmes. This approach was employed primarily with minimally verbal youngsters, a number of whom had previously made only very limited progress in speech-oriented programmes. Studies showed that many were able to learn to convey their basic needs through sign.

One of the initial efforts to teach sign communication skills to "non-speaking" or minimally verbal students occurred at Benhaven beginning in 1971 (Lettick, 1972; 1979). Benhaven, a school in New Haven, Connecticut, served students with ASD or with brain damage, ranging in age from 6 to 21 years. Many were minimally verbal and had failed to demonstrate progress in acquiring communication skills at other institutions. When a deaf child with ASD entered Benhaven, an administrative decision was made to embark on signing lessons for the school's entire staff and to embrace a programme of sign and speech input for all students who were not making progress in acquiring useful speech. Although all the participating students made at least some progress in learning to sign, the range in outcomes was very wide. At the low end were those students whose progress was limited to learning the meaning of only a few signs. In contrast, others were reported to have learned to comprehend and produce numerous signs, to respond appropriately in signed sentences to questions, and to engage in signed conversations. It is not clear how these assessments were made, and from a contemporary perspective, such reports may appear somewhat optimistic; nevertheless at the time they helped to open up opportunities for young people whose abilities were underestimated.

Another important pioneering study of the use of signs to foster communication skills in children with ASD was conducted by Creedon (1973; see also Offir, 1976). The 30 children

in her study were provided with both sign and speech input. All of the children acquired at least some sign communication skills and a number became quite effective users of signs. Forty percent of the participants acquired some spoken language skills as well. Of the participants who acquired some speech skills, seven demonstrated considerable facility in spoken English by forming complex, multi-word utterances. Creedon also reported that those children who showed the greatest progress in acquiring communication skills were typically those who entered the training programme at younger ages. This study is significant because it showed that learning to sign did not preclude the development of spoken language skills and because it underlined the importance of starting intervention programmes early in children's development.

Altogether, the findings from more than 30 studies of sign acquisition in minimally verbal children with ASD have demonstrated the potential effectiveness of sign communication training (Goldstein, 2002; Lal, 2010; Layton, 1987; Tan et al., 2014; Valentino & Shillingsburg, 2011; Wendt, 2009). In most of these studies, the children's teachers or caregivers took individual signs from existing sign languages or sign communication systems and paired them with their spoken language equivalents in their interactions with their children. As a result, the children typically were receiving input in two modalities. The gains in communication skills shown by the children, moreover, could be retained for a long time (Webster et al., 2016), whereas rather poor word retention skills were often seen in participants in vocal language intervention programmes (Gaines et al., 1988). As with the early studies, some of the children were reported to acquire spoken language skill, albeit of a relatively modest nature (Millar, Light & Schlosser, 2006). Only a minority of participants acquired real facility in speech.

Along with their enhanced communication skills, many of the children with ASD who were taught to sign also showed improvements in their adaptive behaviours (Lal, 2010). These included: increased attention span, declines in the number of temper tantrums, a reduction in the incidence of stereotypies (e.g., finger flicking, head banging), greater willingness to engage in group activities, and many fewer soiling incidents. These improvements appear not as the product of direct training in these areas, but are rather associated with the children's greater success in communication through signs. Because many of the children's challenging behaviours (e.g., tantrums, stereotypies) may have served a communication function, the learning of sign communication skills probably reduced the children's need for them.

ADVANTAGES OF THE SIGN MODALITY

A range of explanations has been advanced to try to account for these findings. One area of interest is the auditory-vocal modality itself, as auditoryprocessing problems are very common in individuals with ASD (Baranek, 2002; Condon, 1975). Moreover, vocal stimuli, but not non-vocal sounds (such as environmental sounds), have been found to be processed abnormally in both adults and children with ASD (Gervais et al., 2004; Sperdin & Schaer, 2016). Even highly articulate persons on the Autism Spectrum may find the processing of speech quite difficult, as Temple Grandin, an accomplished scholar has observed (Grandin, 1995; Grandin & Panek, 2013). These findings and other related results have led some

investigators to advance the view that for many individuals with ASD, their visual and kinesthetic abilities are relatively more intact than their auditory-processing abilities (Mirenda, 2014; Mitchell & Ropar, 2004).

Other explanations focus primarily on the visual-gestural modality of signs, which is essentially more conducive to direct instruction than speech. For children with at least some ability to imitate gestures, teachers and caregivers are able to slow down the rate at which they form a sign and may even hold their hands in place until the children are able to copy how the sign is made. Moreover, for those children who experience great difficulty imitating their teachers' sign formation, the teachers could directly mould the children's hands into the correct sign formation. Such direct instruction is simply impossible with spoken words. Another possible advantage is that by teaching the children to sign, teachers and caregivers may indirectly help the children to control their motor stereotypies (e.g., finger flicking, twirling) (Bram, Meier & Sutherland, 1977). By having the ability to communicate through signs, the children may be better able to regulate or control many aspects of their environments. And because these stereotypies or repetitive gestures may interfere with the children's cognitive processing, lowering their frequency may help the children to learn and to communicate more effectively.

Although signs are typically acquired more readily than spoken words by minimally verbal children with ASD, investigators observed early on that certain signs were learned and recalled more easily than others. In particular, highly iconic signs - those signs that clearly resembled the concepts that they stood for - were acquired faster and remembered better than those signs without such transparent ties to their referents (Konstantareas, Oxman & Webster, 1978). These iconic signs often represented meaningful sensori-motor actions or resembled the shapes of objects. This is not to say that non-iconic signs cannot be learned by children with ASD. Rather, it is often the case that the learning of non-iconic signs takes considerably longer to achieve. It is also likely that iconic signs may hold more meaning for the children. This interpretation would be in accord with the results of studies that showed that children with ASD were more likely to imitate meaningful gestures than gestures without clearly discernible meanings (Smith & Bryson, 2007; Vanvuchelen, Roeyers & De Weerd, 2007). (For further discussion of iconicity and sign and gesture learning, see Chapters 3 and 4, this volume).

PROBLEMS IN SIGN ACQUISITION AND USE

Although studies have demonstrated that signs can provide an effective system of communication, they also make it clear that outcomes often varied widely. Whereas some children acquired hundreds of signs and progressed to multi-sign communicative utterances, many children fared less well. They might learn to understand or produce only a few signs, with a limited range of information, despite years of training. Of course, if a minimally verbal child can sign to indicate hunger, or need to use the bathroom, then there will be improvements to the daily life of both the child and their teachers and caregivers (Tan et al., 2014). However, it is important to consider what factors seem to impact on the success of sign learning (see also Chapter 11, this volume).

Delays in Implementing Intervention

One issue would appear to be that sign training often did not begin until after their early childhood and it is not entirely clear what the quality of the input and support was outside formal teaching contexts. Some of the delay in initiating sign training is attributable to parental attitudes and decisions. Many parents often expressed great reluctance to start sign communication training until after their hopes that their children would learn to speak had essentially vanished (Cress & Marvin, 2003). This decision to rely solely on spoken language training was a bad one for several reasons. One reason is that if such speech training proved ineffective, then those children were denied the opportunity to learn a useful non-speech means of communication during their important early years. Also contributing to this late start in the initiation of many programmes of sign communication was the fact that the diagnosis of childhood ASD usually occurred at a much later date than it does today (typically between 2 and 4 years nowadays). Moreover, children with more severe impairments can now often be identified at younger ages; it is those children with more advanced language and adaptive skills that are not reliably identified until 3 years or older (Zwaigenbaum et al., 2016). Earlier diagnosis provides an opportunity to remove an important obstacle to commencing communication training programmes with such minimally verbal children. Recent studies on deaf children with ASD whose first language is sign also promise to deepen our understanding of the role of early input within a sign environment for children who are autistic (Shield, 2014; Shield, Cooley, & Meier, 2017; Shield & Meier, 2012; Shield, Meier, & Tager-Flusberg, 2015; Shield, Pyers, Martin, & Tager-Flusberg, 2016; Shield et al., 2017; see also see Chapter 7, this volume).

The reluctance of many parents to grant approval for their children with ASD to begin a programme of sign communication training appears to rest largely on the parents' mistaken belief that starting to sign was tantamount to admitting that their dream of ever hearing their children's voices was gone forever. However, the notion that if children learn to communicate in one mode (such as sign) then this will impair or preclude their development of communication skills in another mode (such as speech) is fundamentally misguided. Indeed, in recent years it has been recognised that development in one mode often facilitates the development of communication skills in another (Dunst, Meter & Hamby, 2011; Millar, 2009). Rather than precluding spoken language development, learning to sign has often been associated with improvements in speech production and comprehension in both mute and echolalic children with ASD. This finding, moreover, was reported many years ago (Creedon, 1973; see Offir, 1976). In addition, our understanding of language acquisition processes in general has changed substantially in recent decades. Today, the language acquisition of typically developing children is seen as a multi-modal process. That is, typically developing children and their caregivers often make extensive use of pointing and other gestures in their early communicative exchanges, where the use of gesture is predictive of later language development (Rowe & Goldin-Meadow, 2009; Chapters 3 and 4, this volume). Thus, the combining of gestures and spoken utterances is the way that most children learn to communicate.

Deficits in Motor Skills and Imitation

Although using signs to communicate may avoid the auditory-vocal processing difficulties present in many children with ASD, the switch to employing signs also comes with its own set of difficulties. One major difficulty is that children with ASD typically have serious deficits in motor development and in motor processing. Another is that they often have problems imitating the actions of others (see Chapter 3, this volume). In the production and understanding of signs, which rely heavily on motor production and on the visual processing of information, such deficits represent very serious obstacles, and appear to account for some of the widely different outcomes among children with ASD in learning to sign.

Those children who acquired larger sign vocabularies and who formed longer sign utterances were shown to have scored higher on tests of intelligence, and to have better social skills, receptive language abilities, and fine motor skills (Bonvillian & Blackburn, 1991; Gaines et al., 1988). Deficits in motor abilities are now recognised to occur very often in these children and may well be an integral part of the syndrome (Bo, Lee, Colbert & Shen, 2016; Bodison & Mostofsky, 2014; Mirenda, 2008). Both fine and gross motor skills are affected (Chukoskie, Townsend & Westerfield, 2013; Slavoff, 1998) and problems include difficulties in gait, posture, balance and coordination (Gidley Larson & Mostofsky, 2006). These deficits, furthermore, emerge early in the children's development and appear to persist as children get older (Biscaldi et al., 2014).

The finding that motor skill levels were related to success in sign learning (Bonvillian & Blackburn, 1991) subsequently led to more systematic probes of the language (sign and speech) processing and motor functioning of children with ASD. In one study (Seal & Bonvillian, 1997), 14 minimally verbal children with ASD were videotaped while they were interacting with their teachers in sign. Although all of the children made errors in their sign formation, the error rates varied widely across participants. The children who had learned the most signs generally had very low sign formation error rates, whereas the children who learned the fewest signs typically had much higher rates. The examination of the children's sign formations also showed that the children often found the movement parameter of the signs an area of particular difficulty. Following up on this observation, the investigators administered tests of apraxia to 11 of the children. (Apraxia or dyspraxia is a neuromotor disorder that limits one's ability to produce planned, voluntary, and purposeful motor movements in the absence of paralysis.) The children's scores were consistent with a diagnosis of apraxia.

Subsequent studies have confirmed that apraxia impacts on the sign acquisition of both hearing and deaf children with ASD (Page & Boucher, 1998; Bhat et al., 2016). Soorya (2003) found an association between apraxia scores and accuracy of sign production. Page and Boucher found that almost 80 percent of the 33 children they studied showed marked impairment in various aspects of motor functioning. These deficits included oromotor skills (lip and tongue movements), manual skills (object manipulation, making correct handshapes), and gross motor skills (running, hopping). While the children exhibited deficits in all three areas, the most prevalent difficulties were in the oromotor and manual skill areas. The investigators advanced the view that dyspraxia probably played a very important role in the impaired speech and signing of many children with ASD. Performance in oromotor and

manual skills also significantly predicted children's speech fluency in middle childhood and adolescence (Gernsbacher et al., 2008).

In recent years, it has also been shown that difficulties in imitation are very widespread among children with ASD (Shield et al., 2017) and are particularly pronounced in minimally verbal children on the ASD spectrum. Although such deficits may make learning to sign more difficult for children with ASD, it should be noted that these children's initially limited abilities to imitate do appear to improve with increasing age (Biscaldi et al., 2014).

Relationships between Motor Skills and Language and Communication Development

There is strong evidence of close relationships between praxis performance, severity of impairment, comprehension and communicative skills in children with ASD (Dowell et al., 2009; Shield et al., 2017). Gesture and motor imitation abilities have been found to be highly related to measures of vocabulary size, language development, and language usage (Özçalışkan et al., 2017; Slavoff, 1998). Various theories have been advanced in explanation. Neither nonverbal intelligence nor chronological age appear to be implicated (Shield et al., 2017). One view is that children with ASD have problems in forming internal models or representations of actions (Haswell et al., 2009). A second interpretation is that the children have difficulties in motor planning (Lloyd, MacDonald & Lord, 2011; Smith & Bryson, 1994). Another explanation specific to the problem of imitating a visual model is that children with ASD often have a dysfunctional observation matching system (Bernier et al., 2007). Finally, it is also possible that the representations of actions in the working memories of children with ASD may have decayed much more quickly than they do in typically developing children. These views that children with ASD have difficulties forming internal models or that the children's working memories decay more rapidly may help to explain the finding that children with ASD often will successfully imitate only the final action of a gestural sequence (Gonsiorowski, Williamson, & Robins, 2016). For further discussion of praxis and motor skills in ASD, see Chapters 3 and 7, this volume.

Because of the difficulties many children with ASD experience in imitation, moulding of children's hands may offer a more effective way of teaching signs. This is where a teacher or caregiver takes the child's hands in their own and then physically guides the correct sign formation. As the children learn how to form the sign appropriately, the adults gradually reduce their control of the children's hands. Over time, the children should learn to produce their signs on their own (Some children may however resist this approach, which is discussed in some detail in Chapter 13, this volume).

INTERVENTION APPROACHES

The Simplified Sign System

This system was created by Bonvillian, Kissane-Lee, Dooley and Loncke (2018) to help facilitate the development of communication skills in minimally verbal children. At present, it

consists of over 1800 signs that were selected or developed to be more readily formed and remembered than most signs from existing sign languages or sign communication systems. This was accomplished in three ways: (a) the signs in this new system generally consist of a single distinct movement (other than repetitions), as most multi-movement signs were not included; (b) those sign handshapes and movements, which previous research had shown were problematic for children with ASD, were largely avoided by modifying the formation of existing signs or creating new signs without these more difficult handshapes and movements; and (c) by selecting or developing signs that were highly iconic in that they had readily transparent meanings. Although not all of the children learning these new signs are likely to recognise the link between the signs and their underlying concepts or meanings, past research indicates that many of the children are likely to find the Simplified Sign System signs easier to recall than existing signs. Moreover, the children's teachers and parents also are likely to find that this iconic component is very helpful in their learning and remembering of the signs.

Aided Communication

For children who do not seem to progress through speech or sign intervention a number of augmentative and alternative communication (AAC) systems have been developed in recent decades (Beukelman & Mirenda, 2013; Ronski et al., 2015). These approaches often emphasise the use of pictures, real objects, and electronic and speech-generating devices. These systems are based largely on the observation that many of the minimally verbal children with ASD have better visual-processing skills than auditory-vocal skills. These include PECS (Picture Exchange System: Bondy & Frost, 2002; 2009) which has proved efficacious with many children, who are reported to have increased their vocabulary size and frequency of communication (Flippin, Reszka & Watson, 2010; Ganz et al., 2012; Gordon et al., 2011; Preston & Carter, 2009). And for at least a few of the children involved, there may also be an increase in their spoken language skills (Bondy & Frost, 2009), although these gains are likely to be small in magnitude (Flippin et al., 2010). An important difference between PECS and other systems that involve a child's pointing at pictures is that PECS requires that the child interact directly with another person, through the supported prompting to exchange a card for a desired object. However, given the critical importance of pointing in language development, for both typically developing and autistic children (Manwaring et al., 2017; Özçalışkan et al., 2017), it is vital that PECS is employed in a discriminating way - if a child is already pointing to objects or pictures, this natural form of communication needs to be encouraged.

There have been relatively few studies that have systematically compared the use of signs with that of PECS. Such comparison studies, furthermore, are difficult to conduct because children on the autism spectrum often differ widely in their backgrounds and abilities. Anderson (2001) largely overcame these problems by teaching the six children she examined in sessions that alternated between signs and PECS. The children ranged in age from 2 to 4 years. Anderson found that the children, as a group, showed a faster rate of item acquisition and item generalisation with PECS. In contrast, the children showed greater eye contact, more initiation of interaction and communication, and vocalised more frequently with sign training. Of the six participants, three of the young children behaviourally preferred PECS and three preferred to sign. Probing more deeply, Anderson observed that the three participants who

preferred to sign tended to be somewhat older and to have higher levels of gross motor skills and fine motor skills. In light of these trends, Anderson commented that young children with ASD might initially be taught to communicate effectively with PECS and then transition to signs after they had developed higher levels of cognitive and motor functioning.

The results from several other studies (Moodie-Ramdeen, 2008; Nollet, 2008; Tincani, 2004) that compared children's learning of PECS with that of signs largely echoed the findings from Anderson's (2001) early study. Although there were frequently wide individual differences, the following trends were discerned: (a) progress in learning to communicate was faster in PECS than sign; (b) particular children often preferred one approach to another, with some preferring to sign and others preferring PECS; (c) there was a trend for children to vocalise more while signing than when using PECS; and (d) the children's problem behaviours declined over the course of their training programmes as their communication skills improved. In the light of the highly variable outcomes across participants, it is likely that the characteristics of the individual children are driving the outcomes of these intervention approaches rather than the particular systems themselves. It is also important to reflect that these studies focus almost exclusively on request behaviours, so that the effect may also be due to the immediate gratification of the reward provided with PECS. The PECS approach focuses on instrumental success (acquiring an item chosen by the teacher), while more communication-oriented approaches focus on communicative success, that is, on the child being understood and being answered (rather than just given something), and on communication about agents other than the self in I-WANT and I-SEE of PECS. The comparative success of PECS and sign in facilitating a wider range of communicative purposes such as social, commenting, joking, narrating has not been explored to date. At least one study of autistic children has found that those with vocabularies in excess of 20 words did use some of these communication functions (Angeleri et al., 2016).

Advances in technology in recent years are also transforming the way that many severely speech-limited children with ASD are able to communicate. A number of these children have learned to effectively use speech-generating devices (Bornman & Alant, 1999; Schlosser, Sigafoos & Koul, 2009). Applications such as Proloquo2Go™ (Sennott & Bowker, 2009), have essentially overcome the limitation of pre-stored messages. These handheld devices are able to produce digitised or synthetic speech after a user presses a picture symbol or other key. The large storage capacities of these devices, moreover, means that the children do not need to carry with them large communication books or collections of pictures. Using these electronic devices, children on the autism spectrum have been shown to acquire the ability to label things (Lorah & Parnell, 2017) and to make multistep requests (Alzrayer, Banda & Koul, 2017). In teaching the children to use their devices, the investigators often framed their intervention in a behavioural modification approach by breaking down the teaching and learning process to small steps and rewarding the children on their progress. The teachers also would often physically guide the children's hands as the children learned to navigate the system.

Another advantage to using the Proloquo2Go™ application is that children on the ASD spectrum who use it are likely to blend with the peer group, rather than stand out, because the widespread use of portable electronic devices. Opportunities may also be provided for communication modelling and interaction with the children throughout the day than has been the case in the past (Sennott, Light & McNaughton, 2016). Furthermore, typically developing children often have more positive attitudes towards an unfamiliar peer with complex

communication needs who uses these electronic devices than towards a peer who uses a low-technology communication board (Dada et al., 2016).

Investigators have begun to compare the learning and use of signs, PECS, and speech-generating devices (with Proloquo2Go™ application) in children with ASD (Achmadi et al., 2014; Couper et al., 2014; McLay et al., 2015). In each of these studies, children learned all three communication systems to criterion. There was, however, a general acquisition pattern: the children typically reached the criterion faster and maintained performance better with PECS and the speech-generating devices than with signs. The principal explanation advanced by the investigators to account for this pattern was that these two systems relied predominantly on the children's recognition memory skills, whereas the learning and use of signs depended more on the children's recall skills. Fine motor skills, now recognised to be frequently affected children with ASD, are also implicated in these comparisons (Manwaring et al., 2017). Also, when probed as to their preferences, the majority of the children opted to use the speech-generating devices. It should be noted, however, that – once again – the children were being taught to express requests for toys or desired objects: clearly the quickest and easiest way of satisfying desire is to point or touch a picture rather than to form a sign.

These preliminary findings bode well for the continued and expanded use of speech-generating devices (with Proloquo2Go™ application) with hearing children on the ASD spectrum. But it should be recognised that important research work remains to be conducted.

CONCLUSION

This chapter has reviewed the history and application of the use of signs to support communication development in hearing children with ASD. In the future, it will be important to learn which systems results in greater communication success by the children over the long term, as well as whether certain systems are more effective at fostering communication skills for children of different ages and with diverse constellations of abilities. In the light of the very wide range of abilities among children on the ASD spectrum, the recognition of these difficulties in signing deaf populations, and the need to commence intervention as early as possible, it is likely that the optimal course of intervention may involve the use of more than one communication system.

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Chapter 20

HYPERBARIC OXYGEN THERAPY IN SUDDEN SENSORINEURAL HEARING LOSS

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ABSTRACT

Sudden sensorineural hearing loss (SSNHL) is a common clinical entity and defined as a rapid onset of hearing impairment, occurring within three days. It has an audiometric criteria identified as a decrease in hearing of at least 30 dB over three contiguous test frequencies in one or both ears. It has a significant effect on quality of life. As the 88% of SSNHL cases is idiopathic at presentation, there is usually no known exact specific etiologic factor. However, multiple reasons such as vascular compromise and associated cochlear ischemia or viral etiologies, etc. have been presumed and the treatment modalities have been empiric. Although oral steroid therapy is the mainstay treatment in clinical practice, in most of the centers, several different treatment modalities proposed in the literature. Hyperbaric oxygen therapy (HBOT), which has been used for SSNHL treatment since 1979, exposes a patient to 100% oxygen at a pressure level higher than 1 atmosphere absolute in a specially designed sealed chamber. This facilitates a delivery of increased partial pressure of oxygen to the tissues. Based on this fact, it is thought that HBOT may prevent damage caused from ischemia by improving the supply of oxygen to the inner ear and result in an improvement in hearing. This review focuses on the benefits and harms of HBOT in treating SSNHL.

Keywords: sudden sensorineural hearing loss, hyperbaric oxygen therapy, hearing impairment

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INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is a common clinical entity and defined as a rapid onset of hearing impairment in one or both ears, occurring within three days. It has an audiometric criteria identified as a decrease in hearing of at least 30 dB over three contiguous test frequencies in one or both ears. Patients usually admit to the emergency department because of the frightening symptoms such as aural fullness, tinnitus or vertigo. It affects 4000 new people per year in the United States [1-2]. Approximately 88% of SSNHL cases is idiopathic at presentation. However, multiple reasons such as vascular compromise and associated cochlear ischemia, viral etiologies, autoimmune, trauma, schwannoma, demyelinating disease, etc. have been presumed [3]. If the clinicians cannot identify the reason, it is named as idiopathic SSNHL and the treatment is empiric. The exact spontaneous recovery rate cannot be determined, because most of the patients seek medical care in the early period and are treated empirically. The reported rate of spontaneous recovery ranges from 32% to 65% [2, 4]. Although hearing aids are recommended in nonhealing patients with moderate or severe hearing loss, SSNHL has a significant effect on quality of life. There are various different treatment modalities such as systemic and intratympanic steroids, vasodilators, antiviral agents, diuretics, hyperbaric oxygen therapy (HBOT), etc. However, the exact efficacy of these treatments is not known due to the fact that clinicians cannot determine a definitive etiology in most of the cases. Although oral steroid therapy is the mainstay treatment in clinical practice in most of the centers, there are several randomized controlled studies for only HBOT [5-7].

INDICATIONS

The blood supply of inner ear and vestibulocochlear nerve is maintained by labyrinthine artery and also by diffusion through perilymph and cortilymph. The labyrinthine artery has no anastomosis. Therefore, cochlea is very sensitive to ischemia and cochlear hypoxia results in progressive degenerative changes, loss of neurons, and hearing loss.

Vascular compromise and associated cochlear ischemia is one of the possible etiologic factors of SSNHL. HBOT exposes a patient to 100% oxygen at a pressure level higher than 1 atmosphere absolute in a specially designed sealed chamber. This facilitates a delivery of increased partial pressure of oxygen to the tissues. Moreover, it may improve the host reaction against infection and ischemia by reducing hypoxia and edema due to its complex effects on immunity, oxygen transport, and hemodynamics [8]. Based on these facts, it is thought that HBOT may prevent damage caused from ischemia by improving the supply of oxygen to the inner ear, increasing the oxygen tension in perilymph and result in an improvement in hearing. The patency of labyrinthine artery and the rising rate of oxygen tension in perilymph influence the efficacy of HBOT in SSNHL [9].

The clinical guideline of The American Academy of Otolaryngology indicated that corticosteroids and HBOT are treatment options whereas other pharmacologic therapies such as antivirals, thrombolytics, vasodilators, vasoactive substances, or antioxidants should not be prescribed routinely by clinicians. The guideline stated that patient needs multiple 1- to 2-hour sessions (mostly 5 to 10 times) over days to weeks for HBOT which is expensive and

the reports about HBOT had small number of patients and methodological shortcomings. However, they indicated that HBOT may have benefits according to the reported studies and offered HBOT as an adjunctive therapy. They emphasized that it may have better effect in the early period (within 3 months of the onset of SSNHL), younger patients (younger than 50-60 years), and patients with moderate to severe or severe to profound hearing loss [10].

SIDE EFFECTS AND COMPLICATIONS

The possible side effects of HBOT include oxygen poisoning, claustrophobia, temporary worsening of short-sightedness, and damage to sinuses, lungs, and ears due to the pressure changes [10]. The cochrane database review including seven randomized controlled trials, which evaluated the efficacy of HBOT on treatment of SSNHL, reported no systemic side effects [11]. The most common complication of HBOT is middle ear barotrauma [9]. Plafki et al. evaluated the complications and side effects of HBOT in 782 patients with 11,376 sessions. The indication of HBOT in this patients was various. They identified that ear pain or discomfort was the predominant complaint of patients which was seen in 17% of patients. They indicated that this is due to the difficulty equalizing pressure in the middle ear [12]. Fernau et al. evaluated the effect of HBOT on eustachian tube function in patients who undergone HBOT for several different indications and detected eustachian tube dysfunction in 45% of patients [13]. On the other hand, the complication rate in the patients undergoing HBOT for SSNHL is fewer. The concurrent use of systemic steroids might be the reason of this, because steroids may decrease the edema or inflammation which enhances the pressure equalization [10]. Pilgramm et al. reported that three of their participants who were performed HBOT for SSNHL were withdrawn the therapy due to the middle ear barotrauma [14]. Another study observed 6.25% ear or sinus barotrauma in 80 patients undergoing HBOT for SSNHL [15].

CONTRAINDICATIONS

The major contraindications include pneumothorax, severe reactive airways disease, severe congestive heart failure, concomitant doxorubicin or bleomycin therapy, and confinement anxiety [9].

RELATED ARTICLES

The first usage of HBOT in SSNHL in the literature was in 1979 [16]. Since that time, various studies have been performed [5-7, 11]. The improvement of hearing loss with HBOT was indicated in a cochrane database review but the certain level or clinical relevance of this improvement was not clear. This report reviewed seven trials published between 1985 and 2004 including 392 participants in whom 207 received HBOT and 185 was control. The dose of oxygen per treatment session varied between 1.5 and 2.5 ATA as a maximum oxygen pressure and the total course of treatment varied between 10 to 25 sessions in these

randomized controlled studies included in this review. They determined the chance of a 25% increase following HBOT. They indicated that better results may be seen if the patient was treated within 2 weeks of acute onset and the amelioration may be associated with onset severity of the hearing loss [11].

Naiboglu et al. evaluated the effects of three treatment modalities which were intratympanic steroid, systemic steroid, and HBOT on SSNHL treatment. They indicated that patients with profound hearing loss might have better success rate if these three treatment modalities are applied together [17].

Ajduk et al. investigated 93 patients with SSNHL who did not get benefit from steroid therapy. Forty-three of these patients had undergone HBOT as a salvage therapy. They found that although patients with moderate hearing loss (≤ 60 dB) had improvement only at low frequencies (0.25 and 0.5 kHz), patients with severe hearing loss (> 61 dB) had improvement at all frequencies [18].

Alimoglu et al. investigated the impact of HBOT as a salvage treatment of SSNHL by retrospectively reviewing the medical records of their patients who had received a 14-day course of failed oral corticosteroid therapy. They found that the mean gain of pure tone average was more prominent in lower frequencies (0.25 kHz and 0.5 kHz) than higher ones. They proposed that the reason might be the increased vulnerability of the basal turn of the cochlea to damage which leads to a lower predisposition to the recovery [19]. Similar to the report of Alimoglu et al., Muzzi et al. observed higher gains in lower frequencies in 19 patients who received 30 sessions of HBOT after failed medical treatment. However, they did not state the details of applied medical treatment [20].

On the other hand, Cekin et al. studied the efficacy of HBOT on SSNHL as an adjunctive treatment by treating 36 patients with HBOT with concomitant medical therapy with prednisolone (study group) and treating 21 patients with only prednisolone (control group). They compared these two patient groups. Although they found higher success rate in the study group, this difference was not statistically significant. They suggested HBOT as an alternative therapy only if the patients have contraindications for medical therapy such as peptic ulceration, hypertension, old age, etc. [21].

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Chapter 21

AMINOGLYCOSIDE MEDIATED OTOTOXICITY AND HEARING LOSS IN CYSTIC FIBROSIS PATIENTS: AN UNMET MEDICAL NEED

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ABSTRACT

Cystic Fibrosis (CF) is a highly debilitating disease that occurs with high prevalence worldwide. Due to the frequent infections observed in CF patients, physicians recommend antibiotics especially aminoglycosides. However, it leads to cochlear ototoxicity and consequent hearing loss in CF patients. In this commentary, we have highlighted the serious issue of aminoglycoside mediated hearing loss in CF patients. Through this commentary, we want to draw the attention of the clinicians that an active collaboration between pulmonologists and otolaryngologists will facilitate in early detection of hearing loss in CF patients and hence better clinical outcomes. We have also discussed the alternative approaches to avoid aminoglycoside-induced cochleotoxicity in CF patients.

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INTRODUCTION

Cystic fibrosis (CF) is a genetic disease affecting about 30,000 people in the U.S. and more than 70,000 individuals worldwide. It is a progressive and detrimental illness that causes persistent lung irritation and increased susceptibility to air-borne pathogens, with the latter being the primary cause of mortality in CF patients. Despite new advancements in medical technology, CF remains a deadly disease with a median survival of 40 years. As new infections of the airways commonly occur in CF patients, clinicians recommend the use of broad-spectrum antibiotics. *Pseudomonas aeruginosa* is the most prevalent pulmonary pathogen in CF patients. However, the emergence of antibiotic resistance has limited the treatment options. Members of the aminoglycoside family of antibiotics become the last treatment modality in cases of severe and resistant infection in CF patients. However, the use of aminoglycosides (AGs) leads to undesirable side effects including irreversible hearing loss (HL) due to cochlear ototoxicity. A study reported a prevalence of HL as high as 23% in AG-treated CF patients [1]. CF itself is a very debilitating disease, and occurrence of HL further deteriorates the quality of life of CF patients.

MOLECULAR MECHANISMS UNDERLYING OTOTOXICITY

A number of molecular mechanisms have been implicated in the pathophysiology of AG ototoxicity. The mitochondria of epithelial cells in the lateral wall of the cochlear duct act as secondary targets for AGs that can cause mitochondrial damage [2]. This can lead to insufficient energy production in the cochlea inducing sensory cell death and HL. Furthermore, the overabundance of free radicals caused by deactivation of antioxidant enzymes results in higher physiological stress and more sensory cell death, further worsening the problem of HL [3]. Histopathological examination of temporal bone specimens from deceased CF donors exposed to AGs demonstrated a significant loss of vestibular hair cells (both type I and II), dark cells, and spiral ganglion neurons in Rosenthal's canal at the apical turn of the cochlea. A decrease in the area of the stria vascularis at the apical turn of the cochlea was also observed compared to the control group.

ALTERNATIVE APPROACHES TO AVOID AMINOGLYCOSIDE OTOTOXICITY

One strategy to prevent HL in CF patients is to screen for mitochondrial mutations that determine predisposition to AG ototoxicity. In particular, the mitochondrial mutation m.1555A>G can lead to severe and rapid HL when exposed to even low levels of the drugs [4]. Additionally, adjunct therapies should be considered for those receiving AGs. The risk for HL, though lower in the absence of the mitochondrial mutation, remains too high to be negligible. The presence of AGs in the cochlea promotes the formation of reactive oxygen species that do not get cleared adequately. The parallel administration of free radical scavengers such as mannitol can overcome this deficiency. Mannitol have potent free radical scavenging properties when applied to its target site [5]. Albeit more involved than an oral

intake, intracochlear administration of mannitol with direct application to the round window is a feasible approach. Another compound to be considered for preventative therapy is fenofibrate that is used for treatment of lipid disorders appears to protect against gentamicin-induced ototoxicity. Fenofibrate interacts with the DNA promoter regions of genes for catalase and superoxide dismutase-1, anti-oxidant enzymes that prevent the build-up of oxidative stress [3]. By inhibiting the oxidative cascade, fenofibrate directly blocks the production of reactive oxygen species and reduces apoptosis in hair cells. An additional approach in preventing ototoxicity would be to block cellular entry of antibiotics in the cochlea. Phenoxybenzamine, an alpha-blocker mainly used in the treatment of pheochromocytoma, can inhibit uptake of AGs into hair cells [6]. Phenoxybenzamine is the only agent identified so far to abrogate AG interaction with the mitochondria of inner and outer hair cells. Thus, there is a need to explore the efficacy of phenoxybenzamine in preventing AG-mediated ototoxicity in clinical trials.

Since the therapeutic properties of AGs remain unparalleled, a slight change in their design aiming at conserving the therapeutic benefits while minimizing the significant side effects could offer a better solution. Physicians are looking for new ways to develop effective treatment modalities for CF. Indeed, an effective strategy to prevent AG-mediated HL could be found in the structural modification of the antibiotics [7]. The development of modified AG antibiotics is already underway. These designer antibiotics are derived from the structural backbones of existing AGs and are less ototoxic while still maintaining their therapeutic efficacy against pathogens.

CONCLUSION

Bacterial infections are the plague of the 21st century posing a growing challenge to public health. Despite a vast arsenal available to fight them, we often find ourselves left with very few options when it comes to treating CF patients infected by recurring resistant pathogens. As they are cheap, widely available, and broad-spectrum, AGs are often the drugs of choice. Nevertheless, with a significant risk of selective sensory hair cell loss caused by their use, it is imperative to find new venues for providing care for the fragile CF patient population. In our opinion, modified AGs (designer drugs) show the most potential as they maintain efficacy while making these drugs less or non-ototoxic with a broader therapeutic index. Adjunct therapies have shown positive results but are associated with a few problems: (a) the route of administration, although feasible, might not be appreciated by the patients which could result in lower adherence to treatment; (b) the compounds discussed are used as primary treatment for other pathologies and could therefore affect patients with side effects of their own; (c) polypharmacy, the concurrent use of multiple medications by a patient, is a less desirable option.

Otolaryngologists can play a crucial role in developing preventive and therapeutic modalities to preclude AG-mediated ototoxicity in CF patients, which is still an unmet medical need. The detection of HL in the initial stages will lead to early intervention and hence better clinical outcomes. Thus, there is a need to implement routine audiological monitoring for cochleotoxicity in CF centers worldwide. Genetic testing to detect the m.1555A>G mutation in the CF patients will help in predicting their sensitivity to AG-

mediated ototoxicity. Besides, there is a need to develop a consensus for identifying HL in CF patients. Active collaboration between pulmonologists and otolaryngologists holds a great potential to prevent AG-mediated HL in pursuit of improving the quality of life of CF patients and their families.

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Chapter 22

LOW-LEVEL LASER THERAPY: PROGRESS AND FUTURE TRENDS IN HEARING LOSS AND VESTIBULAR DYSFUNCTION

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ABSTRACT

Noise, drug, or age-related disabling hearing loss is a major public health problem affecting nearly 48 million American, 466 million people worldwide, 34 million of whom are children. It poses an annual global cost of US\$750 billion. The main cause of hearing loss is damage to the hearing cells (HC) and recent research is focused on the regeneration of HC by various strategies. Low-level laser therapy (LLLT) has been used to promote healing in damaged cells and as a treatment strategy for damaged nervous systems. Thus, LLLT may be used in the treatment of hearing loss and has been used in the treatment of hearing loss, tinnitus, and hyperacusis. However, the results are equivocal. Some studies in the animal model reported a significant increase in the number and recovery of hair cells and improved hearing with LLLT suggesting its cytoprotective effect while others reported no significant improvement with LLLT. Similarly, the studies in clinical settings have reported improvement in patients with tinnitus and hyperacusis. The results showed that LLLT is effective short-term treatment in alleviating tinnitus in patients with noise-induced hearing loss but for a short period of time and its impact may be fade over time. Patients with hyperacusis have also reported better tolerability of general noise with LLLT but were associated with reactive tinnitus and/or pain. However, no clinically statistically significant differences with LLLT in patients with hearing loss has also been reported. Thus, the role of LLLT in the treatment of hearing loss warrants further research. This chapter is focused on discussing the role of LLLT in the treatment of hearing the loss in animal models as well as in clinics.

INTRODUCTION

Noise, drug, or age-related disabling hearing loss is a major public health problem affecting nearly 48 million Americans, 466 million people worldwide, 34 million of whom are children. It poses an annual global cost of US\$750 billion. Death of the auditory hair cells (HCs) induces the trans-differentiation of adjacent supporting cells (SCs) into new HCs in non-mammalian vertebrates, however, this capacity is absent in juvenile and adult mammals and lead to a permanent hearing loss [1-3]. Thus, it is important to protect the cochlear structure from ongoing degeneration to prevent further hearing loss. A cochlear implant is the only effective treatment available for hearing loss at present [4]. Regeneration of the drug- or noise-induced damaged hair cells and the gene therapy are the current area of research, however, no definitive strategies have been investigated till date [5-8]. Thus, investigation of a definitive treatment warrants further research. Since low-level laser therapy (LLLT) is useful in the treatment of inflammation, swelling, regeneration, and wound healing, the combinational therapies of hearing cell regeneration with LLLT may be a potential therapeutic strategy [9-11]. LLLT (laser energy in the red and near-infrared light spectrum) has been used for the treatment of pain, swelling, and postsurgical tissue repair for years. The therapeutic effect of LLLT is due to stimulation of mitochondria in the cells to produce more energy through the production of adenosine triphosphate [9]. The advantage of LLLT in the regeneration of the hair cells may also be due to the notion that both cochlear hair cells and neural cells are from the same developmental origin. LLLT may have a beneficial effect in the treatment of hearing loss as it has become a popular strategy for the treatment of injuries and/or pathologies to the nervous system. Laser therapy is effective in wound healing, inflammation reduction, and nerve regeneration. The effectiveness and popularity of LLLT are due to its capability to penetrate soft tissue and the deepest part of the body without damaging non-target soft tissues depending on the wavelength [12]. The effects of LLLT on hearing loss and tinnitus have been studied by various researchers, however, the results have been equivocal. This chapter focuses on the use of LLLT to treat impaired hearing and vestibular dysfunction.

ROLE OF LLLT IN HEARING LOSS (ANIMAL MODELS)

The hypothesis that LLLT may be useful in repairing the damaged hair cells and improving cochlear function have been studied by various researchers and it was found that anatomic and physiologic changes in the cochlea can be induced by laser stimulation. Rhee et al. [13] studied the effects of LLLT on hair cell survival following gentamicin exposure using organotypic cultures of the cochlea of rats and reported that LLLT promotes hair cell survival after gentamicin damage. The organotypic cultures of rat cochlea were irradiated with a laser (wavelength of 810 nm at 8 mW/cm² for 60 min per day with 0.48 J/cm²) for 6 days. After laser irradiation to the gentamicin-treated group, a significant increase in the number of hair cells suggested the beneficial effect of LLLT on the recovery of cochlear hair cells. Further, the same group using the rat model of noise-induced hearing loss irradiated with 830-nm diode laser once a day for 10 days with a power density of 900 mW/cm² and a fluence of 162 to 194 J reported significantly increased number of hair cells in middle and basal turns and

significantly improved hearing. A significant improvement in hearing thresholds of the auditory brainstem responses (ABR) which were measured before treatment, after gentamicin, and after 10 days of LLLT and an increase in the hair-cell count was noticed. No adverse tissue reaction on the intact tympanic membrane was found at the end of the experiment [14, 15]. These results suggest that rat hair cells were repaired with LLLT following noise exposure without any adverse reaction. In another study, Tamura et al. [16] studied the therapeutic effect of LLLT on noise-induced hearing loss (NIHL) using an NIHL model of Sprague–Dawley rats. After intense noise trauma, the right ear of the rats was irradiated with 808 nm diode laser at an output power density of 110 or 165 mW/cm² for 5 consecutive days for a 30 min period. LLLT irradiation resulted in accelerated recovery of auditory function (ABR) and significantly higher OHC survival rate (as indicated by the morphological studies) in LLLT treated group compared to the control group at 2, 4, 7 and 14 days after noise exposure. A significant reduction in the inducible nitric oxide synthase (iNOS) and cleaved caspase-3 was observed 165 mW/cm² power density. These results suggested the cytoprotective effects of LLLT against NIHL via the inhibition of iNOS expression and apoptosis.

The basilar membrane, which is tonotopically tuned based on the spatial variation of its mass, stiffness and damping, consist of collagen fibers and these fibers define its biophysical properties. Hence, alteration in collagen fibers density and organization may affect cochlear tuning. Wenzel et al. [17] using guinea pig studied the effect of LLLT on collagen within the basilar membrane using histological analysis. Excised guinea pig cochleae stained with trypan blue were irradiated with a 600 nm and 5 J/cm² pulsed dye laser and collagen organization was analyzed using polarization microscopy. A reduction in birefringence within the basilar membrane and other stained collagen-containing structures directly proportional to the laser pulse was found with laser irradiation. The study reported immediate alterations in collagen organization within the cochlea after laser irradiation and these alterations may affect cochlear tuning. Lee et al. [12] studied the effectiveness of simultaneous bilateral laser therapy compared with unilateral laser therapy on NIHL in a NIHL Sprague-Dawley rat model by exposing them to narrow-band noise at 115 dB SPL for 6 h and then laser irradiation (diode laser with 808 nm wavelength, 165 mW/cm², 594 J) for 60 mins for 15 days in both ears. ABR (4, 8, 12, 16, and 32 kHz) was measured after each irradiation and cochlear hair cells were counted after the 15th such irradiation. The study found that 5% of the laser energy from one ear reached the contralateral cochlea. Both unilateral and bilateral laser therapy decreased the hearing threshold after noise overstimulation, but bilateral laser therapy showed faster functional recovery, however, no difference was found in the final hair cell survival and the endpoint ABR results.

Ouabain is a cardiac glycoside and causes auditory neuropathy by impaired auditory nerve function. Lee et al. [18] induced the auditory neural degeneration sparing the sensory epithelium with local ouabain application in gerbils and investigated the therapeutic effect of photobiomodulation (PBM) after seven days of laser irradiation based on the notion that laser therapy enhances nerve growth or induce axonal regeneration. Histological analysis of cochlea mid-modiolar sections after treatment showed damaged spiral ganglion cells, neurofilaments, and postsynaptic puncta. The authors did not observe any change in distortion product otoacoustic emission (DPOAE) suggesting no change in outer hair cell function, however, ABR thresholds were increased after ouabain application. Laser irradiation after ouabain treatment lowered the ABR thresholds compared to only ouabain treated group.

Laser treatment also showed a higher number of spiral ganglion cells, a higher density of neurofilaments, and higher number postsynaptic puncta counts in the laser treated group compared with ouabain application group. Alleviation of the hearing loss with recovered auditory function and improved histologic outcome suggests the rescue effect of PBM and its potential for inner ear diseases accompanied by spiral ganglion degeneration. These results suggests the potential of LLLT in restoring the hearing loss by increases HC regeneration and the possibility of LLLT as a therapeutic promising option in hearing field.

ROLE OF LLLT IN HEARING LOSS IN HUMAN

The effects of LLLT on hearing loss and tinnitus have been investigated in humans. The reported studies in the literature showed equivocal results; some studies showed that LLLT improved the hearing thresholds and tinnitus symptoms [19-23], while others found no significant effect of LLLT [24-28]. The discrepancy in results might be due to study design, subject characteristics, LLLT methodology, and outcome measures used to assess the effects of LLLT. Goodman et al. [29] using a randomized, double-blind, placebo-controlled design studied the effect of LLLT on hearing loss, speech understanding, and/or cochlear function in adults. LLLT was applied three times in a week by shining low-level lasers for five minutes onto the outer ear, head, and neck. LLLT was applied using an Erchonia EHL laser with a hand-held probe with two laser diodes and a main body, one producing light of 532 nm wavelength (green; constant) and the other diode producing light of 635 nm wavelength (red; pulsed with frequencies of 15 and 33 Hz alternating every 30s) with both diodes producing energy levels of 7.5 mW (class IIIb). Pure-tone audiometry, the Connected Speech Test, and transient-evoked otoacoustic emissions were carried out immediately before the first treatment and immediately after the third treatment. No clinically and statistically significant differences on auditory functions were found between treatment and control group. These results suggest that LLLT is not effective in restoring hearing loss. In another study, Zhou GY [30] investigated the therapeutic effect of LLLT on acupoint and external auditory canal combined with auricular point sticking (APS) on moderate and severe sudden deafness. After one and two sessions of LLLT, fifteen days each, the therapeutic effect was better after the second session compared to one session only. Decreased frequency audiometry and improved auditory function were found after LLLT on acupoint and external auditory canal combined with APS and electroacupuncture and the therapeutic effects was better with prolongation of treatment time. Further, Lapchenko et al. [31] evaluated the efficacy of supravascular laser irradiation of blood for the treatment of cochleovestibular disorders and to confirm the beneficial effect of LLLT in patients with acute hearing disorders. 165 patients with neurosensory impairment of hearing and Meniere's disease were irradiated with supravascular (extracorporeal) laser. The study finds the effectiveness of LLLT in alleviating the labyrinthine hydrops in patients with Meniere's disease, however, it was less efficacious for the management of long-standing hearing impairment and chronic hearing loss. The authors conclude that LLLT may be effective in preventing the development of these conditions. The potential role of laser therapy in improving auditory function and other diseases of the ear in human subjects indicates the potential therapeutic role of LLLT in hearing restoration. However, discrepancies in results warrant further research.

TREATMENT OF TINNITUS

Tinnitus is listening to the sound without any external auditory stimulus. At least one episode of tinnitus is experienced by about 15% of the general population. The prevalence of tinnitus increases by age and reaches 85% in individuals older than 60 years and is more prevalent among individuals with hearing disorders. Tinnitus may lead to such complications as depression, irritability, sleep disorders, and loss of concentration. Thus, treatment of tinnitus is a must to get rid of unwanted hearing and associated complications. Several modalities for the treatment of tinnitus have been proposed, however, an effective standard treatment is still to be confirmed [32]. In this regards, as there is lack of a definitive therapy, LLLT might be a potential therapeutic option. Mollasadeghi et al. [32] evaluated the effect of LLLT on tinnitus accompanied by NIHL (noise-induced hearing loss) using a double-blind randomized clinical trial and found that LLLT is effective in alleviating tinnitus in patients with NIHL, however, the effect fade after 3 months. LLLT with wavelength of 650 nm and intensity of 5 mW was irradiated to the ear via mastoid bone for 20 sessions every other day with each session of 20 minutes. Pure-tone audiometry at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz frequencies and tympanometry were performed after LLLT. Tinnitus was assessed by visual analog scale, tinnitus handicap inventory, and tinnitus loudness at baseline, immediately and 3 months after the intervention. Similarly, Drvis et al. [33] studied the effect of LLLT in treating chronic subjective tinnitus. 42 patients with unilateral or bilateral tinnitus for more than 3 months were treated with LLLT (wavelength 650 nm, output 50 mW) for twenty minutes per session, 10 sessions, 2-3 sessions per week. Pre and post-LLLT tinnitus was measured with the Tinnitus Handicap Inventory (THI) and Visual Analog Scale (VAS). No statistically significant difference in pre and post LLLT in THI in this study suggest that LLLT is not an effective modality for the treatment of tinnitus. In another study, Mirvakili et al. [34] in a cross-sectional study on 120 patients with tinnitus and sensorineural hearing loss (SNHL) studied the therapeutic effect of LLLT on intractable tinnitus. The experimental group received LLLT with a low-level laser device (TINNImed, made in Switzerland) with an intensity of 5mW and wavelength of 650 nm for 20 sessions of 20 minutes. THI and VAS were used to evaluate the severity of patients' symptoms and Audiometric tests for severity and frequency of tinnitus. The study found a statistically significant mean difference of severity of tinnitus between the experimental and control group at the end of the study and 3 months after completion of treatment. The VAS and THI mean differences were statistically significant between the experimental and control group, however, were not statistically significant after 3 months after completing the study. These results suggest the effectiveness of LLLT for short-term treatment of tinnitus caused by SNHL.

To assess the effect of LLLT on chronic cochlear tinnitus, Dehkordi et al. [35] conducted a prospective, double-blind, placebo-controlled study with 66 patients equally divided in two groups; one receiving active LLLT and other inactive dummy treatment. LLLT (5 mV with a wavelength of 650 nm) was irradiated for 20 minutes a day, 5 days a week, for 4 weeks. Tinnitus Severity Index (TSI), a subjective 10-point self-assessment scale for tinnitus loudness, and Tinnitus Evaluation Test (TET) was used to evaluate the degree of tinnitus before and after the treatment. Authors did not find any statistically significant difference in the number of patients experiencing a reduction in TSI values, a reduction in subjective self-assessment scores, and a reduction in the loudness and frequency of tinnitus. The study

concluded that 5-mV LLLT does not have any therapeutic effect in improving hearing thresholds or for treating tinnitus regarding age, sex, environmental noise level, and the duration of tinnitus. Further, Salahaldin et al. [23] in a prospective clinical study investigated the therapeutic effectiveness of LLLT in 65 patients aged 15–76 years with chronic unilateral or bilateral tinnitus and not responding to conventional therapy. Transmeatally laser irradiation with 5mW laser with a wavelength of 650 nm applied for 20 minutes once daily for 3 months showed significant improvement in tinnitus symptoms in 56.9% patients. Out of this 6.15 % of patients reported full improvement, 16.9% of patients reported moderate improvement, and 33.8% of patients reported mild improvement. Improvement in dizzy spells was also reported in 27.7% (mild improvement) and 16.9% (full improvement) patients. 20% of the patients reported the mild side effects of LLLT which disappeared within a few days. These results are suggestive of the effectiveness of LLLT in the treatment of chronic tinnitus.

ROLE OF LLLT IN GENE THERAPY FOR HEARING LOSS

Hearing loss affects millions of people and genetic mutations play a direct role in both congenital and late-onset cases of SNHL. At present, the cochlear implant is the only available effective treatment for moderate to severe hearing loss. Since mutation plays a direct role in SNHL, manipulating the causal gene by gene- and cell-based therapies are the current areas of research to develop a therapy which potentially may preserve or restore hearing with more natural sound perception. Preclinical studies of cochlear gene therapy have made major progress, however, there are hurdles (such as the delivery of the gene to the inner ear) and the outcome is not effective, and efficacy of therapy is low. Thus, there is a need for better strategies for gene therapy to be more effective [4]. Chang et al. [36] using the HEI-OC1 cells investigated the effect of PBM on gene therapy to see whether LLLT improves the rate of adenovirus (Ad)-mediated viral delivery. HEI-OC1 cells treated with Ad viral vector carrying green fluorescent protein (GFP) were irradiated with 808 nm at 15mW for 15 min LLLT at 2 h and again at 24 h. The study results showed increased epifluorescence of GFP expression/cell in 1 μ L Ad-GFP + LLLT, and 3 μ L Ad-GFP + LLLT groups compared to 1 μ L and 3 μ L Ad-GFP cells. These results are suggestive of the notion that LLLT enhanced the gene delivery of Ad-mediated viral transduction and combination of Ad-mediated viral transduction with LLLT may be a promising tool for gene delivery.

ROLE OF LLLT IN VESTIBULAR DYSFUNCTION

Gentamicin used as an antibiotic to treat infections is a known vestibular toxic agent and cause varying degrees of balance problems. Because PBM has the ability to reach deep inner ear organs, Lee et al. [37] using a rat model investigated the effect of PBM on vestibular toxicity and balance dysfunction caused by gentamicin. The study reported minimized damage from gentamicin treatment evidenced by slow harmonic acceleration (SHA) asymmetry and recovered gain in the laser treated ear compared to untreated ear. Further, increased hair cell density and epifluorescence intensity in laser-treated cupulae on histopathology suggested the beneficial therapeutic effect of laser therapy. Similarly, the

beneficial effect of LLLT on vestibular dysfunction was reported by Rhee et al. [38] who evaluated the adverse effects of transmeatal LLLT on OHC and IHC structures and its effect on gentamicin-induced unilateral vestibulopathy in guinea pigs. The group also measured the penetration rate of transmeatal LLLT into the perilymphatic space of cochlea through a tympanic membrane and did the histopathologic analysis of ear canal skin and eardrum to assess the damage by LLLT. Laser of 830 nm wavelength with an output power of 80 mW for 30 min (144 J/cm^2) irradiated into the left ear through the external ear canal for 5 days and daily for 2 weeks. The animals received the sinusoidal oscillation about a vertical and off vertical axis for 5 days after injection. Post-LLLT, no hearing loss and no damage to ear canal skin and eardrum suggested the restoring capacity of LLLT function on dysfunction in guinea pigs. The study found 8% penetration rate of LLL through the drum and of this 5% was penetrated the perilymphatic space. Further, it was found that the left side gains of the LLLT treated group was significantly higher than the control group, however, the gains of the right ear in both groups were not significantly different.

CONCLUSION

LLLT has been found beneficial in the treatment of inflammation, decreasing swelling, wound healing, hair transplant, and alleviating side effects of chemotherapy. Based on the capacity of LLLT to penetrate the deep tissue without any side effects, LLLT may be beneficial in restoring hearing loss. Based on the results of above discussed studies it is conceivable that laser irradiation may have therapeutic benefits for patients with hearing loss, tinnitus, Meniere's disease, and vestibular dysfunction. However, discrepancies in results of various studies and equivocal results in others warrant further research.

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VOLUME 2

Chapter 23

NOVEL DEAFNESS GENES AND MUTATIONS IDENTIFIED BY NEXT GENERATION SEQUENCING

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ABSTRACT

Identifying the genetic basis of deafness provides crucial information for diagnosis, intervention and treatment of the disease. Non-syndromic sensorineural hearing loss, however, are extremely heterogeneous, with both common and rare forms occurring due to mutations over estimated 500 genes. Due to the larger number and presumably low mutation frequencies of those genes, it would be highly expensive and time-consuming to address this issue by conventional gene-by-gene Sanger sequencing. Next generation sequencing (NGS) has become a highly efficient strategy for identifying novel causative genes and mutations involved in heritable disease. Both simple nonsyndromic and complex syndromic forms of hearing loss can be resolved efficiently using NGS, especially in small families with distinct and interesting phenotypes that were once too small to map. To date, more than a dozen syndromic or nonsyndromic deafness genes have been identified using targeted genomic enrichment and NGS. Here, we summarized novel deafness genes and mutations identified by NGS methodologies.

INTRODUCTION

To date, more than 100 genes and 100 genetic loci have been implicated in NSHL (<http://hereditaryhearingloss.org/>). The marked heterogeneity of genetic hearing loss can be explained by the complexity of the auditory system, which requires coordination of multiple

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processes involving the inner ear and nervous system. A defect in any part of this complex chain of events can lead to hearing impairment. For many decades, linkage analysis has been the most powerful and widely used strategy to identify the gene defects responsible for inherited disorders. However, this approach is time consuming and requires the availability of cohorts of homogeneous and informative, possibly large families and a large proportion of NSHL remain genetically unexplained.

These limitations, however, may be overcome by the next-generation sequencing (NGS) technologies.

NGS offers an unprecedented ability to identify rare variants and new causative genes. Several next generation sequencing platforms allow for a DNA-to-diagnosis protocol to identify the molecular basis of inherited non-syndromic hearing loss, including whole genome sequencing (WGS), whole exome sequencing (WES) and targeted deafness gene capture.

Updated guidelines from the American College of Medical Genetics and Genomics (ACMG) recommend that clinicians consider NGS when testing for genetic causes of hearing loss [1]. The guideline, which is built on guidelines issued in 2002, include panel tests targeted at genes related to hearing loss, whole exome sequencing, and whole genome sequencing after negative results are returned on initial single-gene testing indicated by a patient's family medical history and presentation.

WHOLE GENOME SEQUENCING

Whole genome sequencing (WGS) by next generation sequencing technologies has the potential for simultaneous, comprehensive, differential diagnostic testing of monogenic illnesses.

In 2003, the cost of sequencing a single human genome was estimated to be 2.7 billion dollars, that price had dropped to 4,000 dollars by 2012, and it is anticipated that this cost will soon be 1,000 dollars. Clinical use of WGS by NGS has taken at least a month. Researchers already have been able to help clinicians aid some children born with rare birth defects by sequencing and analyzing their whole genomes to diagnose and treat their illness [2].

This is only the beginning of the whole genome sequencing era, which has the potential to revolutionize medicine.

However, there is no report about application of whole genome sequencing on the inherited non-syndromic hearing loss. There are major obstacles to the clinical implementation of WGS, such as hidden costs, issues surrounding sequencing and analysis, quality assurance and standardization protocols, ethical dilemmas, and difficulties with interpretation of the results. With the availability of human WGS data from many individuals, it's now clear that two unrelated individuals have at least two million differences in their genomic DNA sequences [3]. The full potential of WGS can be realized only when we gain a much better understanding of the functions of noncoding regions. WGS should be carefully implemented in the clinic to allow the realization of its potential to improve patient health in specific indications.

WHOLE EXOME SEQUENCING

Approximately 85% of disease-related mutations in Mendelian disorders have been found in the protein-coding region, although this portion constitutes only approximately 1% of the human genome [4, 5]. WES has become a highly efficient strategy for identifying novel causative genes and mutations involved in heritable disease.

Over 1,778 publications since 2009 whose abstracts contain the term “whole exome sequencing”, confirm the success of exome sequencing as a new and effective technological paradigm within human genetics.

Table 1. List of genes and mutations related with non-syndromic hearing loss identified by WES

GENE NAME	Mutation (protein)	References
<i>OSBPL2</i>	p.Gln53Argfs*100 p.Leu195Met	[6]
<i>TBC1D24</i>	p.Ser178Leu	[7]
<i>TNC</i>	p. Thr 1796Ser p.V1773M	[8]
<i>ELMOD3</i>	p.Leu265Ser	[9]
<i>KARS</i>	p.Asp377Asn p.Tyr173His	[10]
<i>GRXCR2</i>	c.714dupT	[11]
<i>ATP1A2</i>	p.Val191Met	[12]
<i>ADCY1</i>	p.Arg1038X	[13]
<i>BDP1</i>	p.*2625Gluext*11	[14]
<i>EPS8</i>	p.Gln30*	[15]
<i>PNKP</i>	p.Gly292Arg	[16]
<i>PCDH15</i>	p.Met65Ile p.Ser404Arg	[16]
<i>CDH23</i>	p.Pro240Leu p.Glu1595Lys p.Asn342Ser	[17]
<i>POU4F3</i>	p.Arg326Lys	[18]
<i>MYO15A</i>	p.Ser1481 Pro p.Gln1425X p.Ala1551Asp IVS11 + 1 p.Arg2146Q	[19, 20, 21]
<i>TMC1</i>	p.Ser530X p.Gly197Arg p.Gln391X	[19, 22]
<i>ACTG1</i>	p.Met305Thr	[23]
<i>LOXHD1</i>	p. Arg1494X p. Glu955X	[19]
<i>GIPC3</i>	p.His170Asn	[19]
<i>ILDR1</i>	p. Gln 274X	[19]
<i>MYO7A</i>	p.Gly2163 Ser	[19]
<i>TECTA</i>	p. Tyr 1737Cys	[19]
<i>TMPRSS3</i>	p.F13Lfs*10	[19]
<i>TRIOBP</i>	p. Arg785 Ser fs*50	[19]

Whole exome sequencing has proven useful for identifying the molecular defects underlying single gene disorders (Mendelian inheritance), as well as some genetically heterogeneous disorders, such as inherited non-syndromic hearing loss.

Inherited non-syndromic hearing loss can be resolved efficiently using WES, especially in small families with distinct and interesting phenotypes that were once too small to map using linkage analysis.

Recently, there have been many successful applications of WES in identifying the causative genes and mutations of inherited non-syndromic hearing loss (Table 1).

To date, 10 non-syndromic deafness genes and more than 30 novel causative mutations were identified by WES (Table 1). These studies show that WES, followed by verification and functional and immunolabeling examinations, can reveal critical disease-causing genes from small pedigrees.

Even with the rapid maturation of this field, there are a number of areas that are still many work in progress: (1) WES fails to solve a substantial proportion of presumably Mendelian phenotypes [24]. (2) There is tremendous interest understanding the contribution of rare variation to the genetic basis of common disease. Many such studies have been initiated using WES, but are still ongoing as they require other samples to testify the results. (3) The discrete prioritization of all protein-altering variation over all other variations has clearly proven to be useful, but is undeniably crude.

TARGETED DEAFNESS GENE CAPTURE AND NGS

The popular application of targeted gene capture is all of the genes involved in causing hearing loss, including all exons, exon/intron boundaries and promoter sequences could be fully sequenced on a diagnostic platform to produce a specific genetic test for hearing loss. Targeted deafness gene capture combined with NGS is suited to identify the causative mutations of non-syndromic hereditary hearing loss owing to the following advantages: 1) comprehensive coverage of large numbers of genes and large genes associated with the disease; 2) significant cost saving; 3) higher sequencing accuracy because of deeper achievable coverage; 4) a significantly shorter turnaround time and 5) more convincing dataset by excluding other deafness genes [25].

To date, more than 100 human genes implicated in non-syndromic hearing loss are confirmed [25]. Approximately 100Gbp of sequencing is needed to obtain NGS results for one human genome (~3.2G bp) at about 30× average coverage. Targeted gene enrichment typically increases this proportion by at least 1,000 fold [26, 27, 28].

Therefore, the same sequencing capacity can theoretically be used to sequence more than 1,000 samples for a panel of genes associated with deafness.

The recent studies demonstrated the feasibility of conducting diagnostic tests for all deafness-related genes by targeted gene capture and NGS [26, 27]. Its success in research has already resulted in its translational uses in clinical care, and many of them are for diagnostic mutation detection of focused panels of disease genes.

OtoSCOPE (Otolological Sequence Capture Of Pathogenic Exons) is the first massively parallel sequencing platform that utilizes targeted sequence capture and NGS for genetic testing of hearing loss [27]. It has been developed by the University of Iowa and is being

used in a research setting to fully sequence all exons of 57 deafness genes (http://www.healthcare.uiowa.edu/labs/morl/index_CDS.htm). At this stage in its development various methods of targeted sequence capture and NGS are being compared to determine which combination has the greatest level of sequence coverage. Otogenetics Corporation in the US is currently offering a genetic mutation testing service using targeted sequence capture and NGS for the detection of variants in 131 known deafness genes for approximately \$500 per sample (www.otogenetics.com).

Richard J.H. Smith, MD, Director of the Molecular Otolaryngology and Renal Research Laboratories at the Iowa Institute of Human Genetics at University of Iowa in Iowa City, is a proponent of panel testing for hearing loss. His lab offers a test that covers 90 genes known to cause hearing loss, which he suggests over any initial single-gene test. Because panel tests offer more depth of coverage in genes associated with hearing loss, they are superior to WES at some extent, which looks at 20,000 genes and may miss parts of them.

The drawbacks of panel tests are these tests that use disease-targeted exon capture focused on specific genes may only sequence a subset of the genes known to cause hearing loss, and there is limited knowledge of which genes are involved in hearing loss.

CHALLENGE AND FUTURE

Applications of NGS technologies are now beginning to enter clinical practice. Interpreting the data and translating the research results into applications that improve healthcare is still challenging. Filtering through the millions of variants in an individual's genome for the pathogenic mutation seems to be the most urgent task at hand. Another important aspect is the concurrent development of genetic counseling capabilities to interpret the large amount of data revealed by NGS for clinical use. In the near future, physicians may combine a past medical history and family history with NGS diagnostic data to identify disease predisposition variants and variants that affect drug metabolism in individuals.

Although NGS-based molecular diagnostic tests are still in their infancy, they have demonstrated excellent clinical utility for single-gene disorders. With further developments in NGS technologies for data generation and with more effective bioinformatics tools for data analysis and clinical extraction, the full potential of WES/WGS that we expect to be revealed in the coming years will greatly enrich and empower the practice of genomic medicine beyond the rare single-gene disorders. The improvements in patient care demonstrated in recent studies justify all effort and cost for moving these new and exciting approaches into molecular diagnostics practices.

In our opinion, WES, WGS, and targeted deafness gene capture should remain as options to be considered for inherited non-syndromic hearing loss and be used according to a patient's specific conditions. Alternatively, a combined approach can be used to capture all variety of genomic variations.

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Chapter 24

THE MOLECULAR PATHOGENESIS OF DOMINANT DEAFNESS-ONYCHODYSTROPHY (DDOD) SYNDROME

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ABSTRACT

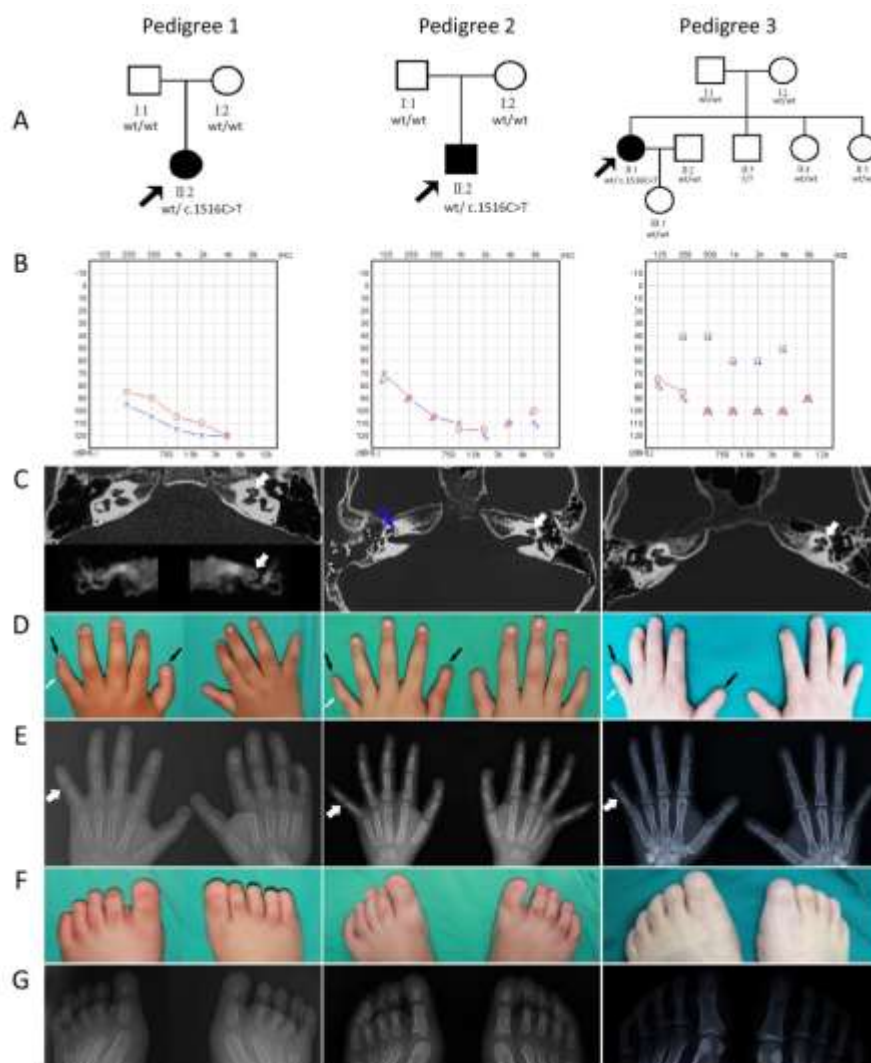
Dominant deafness-onychodystrophy syndrome (DDOD, MIM 124480) is a type of ectodermal dysplasia characterized mainly by congenital deafness, absent nails and/or toes with variable presence of brachydactyly, hypoplastic distal phalanges, and bulbous distal phalanges. Using the whole-exome sequencing approach, we identified a de novo mutation (c.1516 C>T [p.Arg506X]) in ATP6V1B2 as the cause of DDOD syndrome in three independently identified individuals. Molecular epidemiology analysis showed that the ATP6V1B2 p.Arg506X mutation was not present in 1053 ethnically matched normal hearing controls. ATP6V1B2 encodes a component of the vacuolar ATPase (V-ATPase, also known as H⁺-ATPase), a multisubunit enzyme that mediates acidification of eukaryotic intracellular organelles. We generated an Atp6v1b2 knockdown mouse model and found that Atp6v1b2 deficiency leads to severe sensorineural hearing loss. In vitro pathogenic evaluation showed that the ATP6V1B2 p.Arg506X mutation is a dominant haplo-insufficient mutation that caused abnormal acidification in the lysosomes. The acidification defect in lysosomes may cause decreased activity of acid-dependent hydrolases and thus hydrolytic dysfunction of the lysosome affects development of multiple systems such as the inner ear, phalanx, and nail in the DDOD syndrome. The findings provide the molecular basis for DDOD genetic diagnosis as well as exciting developments in future therapeutic interventions.

INTRODUCTION

Dominant deafness-onychodystrophy syndrome (DDOD syndrome, MIM 124480) is characterized mainly by congenital sensorineural hearing loss, and accompanied by dystrophic or absent nails. In some individuals, conical and hypoplastic teeth may also be observed. Prominent differences between DDOD and DOORS syndrome (deafness, onychodystrophy, osteodystrophy, intellectual disability and seizures, MIM 220500) are the intellectual disability and seizure aspects of DOORS [1]. *TBC1D24* mutations were verified as a cause of DOORS syndrome recently [2]. The association between deafness and onychodystrophy segregating as an autosomal dominant condition was first recognized in 1962 by Robinson et al. [3], and later was confirmed by Kondoh et al.[4] as well as White and Fahey [5]. To date, ten families with DDOD syndrome in various ethnic populations have been reported [2-9]. However, the molecular etiology of DDOD remains unknown. In this chapter, we report the identification of a common *de novo* mutation in *ATP6V1B2* among three independent Chinese families with the DDOD syndrome. We will present evidence supporting that *ATP6V1B2* is essential for hearing and that the identified mutation causes abnormal acidification in the lysosome.

Pedigrees and Clinical Evaluations

Three DDOD pedigrees were collected in China during the year 2011~2012. The DDOD pedigrees 1 and 3 were ascertained from Shanxi province, and pedigree 2 was from Jilin province of mainland China. The probands displayed identical phenotypes including severe congenital sensorineural hearing loss, absence of all toe nails, absence of nails on the little finger and thumb, phalanx deficiency of the little finger, onychodystrophy-like malacia, and pitting of the middle three fingernails (Figure 1). The gross inner ear structure was normal in all probands in this study as assessed by magnetic resonance imaging and high-resolution temporal bone computed tomography (Figure 1). All three individuals had unilateral cochlea implantation at the ages of 2.5, 2, and 18 years, respectively. Cognitive evaluation was performed using selected subclasses from a Chinese revised version of Griffiths Mental Development Scales (GMDS, 0-8 years of age) prior to cochlea implant operation[10]. The normal range of General Quotients of the Griffith test was above 70 in non-syndromic Chinese hearing loss individuals, and cases 1 and 2 scored 75 and 77, respectively. After cochlea implantation, language rehabilitation in the probands from pedigree 1 and pedigree 2 showed no distinct difference compared to other nonsyndromic hearing loss individuals. Although the proband in pedigree 3 had prelingual hearing loss and had received a cochlea implant as an adult, she made significant improvement in speech perception in both listening and pronunciation skills due to speech training in a language rehabilitation school from the age of 3 years. This successful language rehabilitation in the three DDOD probands further confirmed their normal mental development.



- (A) Pedigree of three DDOD families and segregation of the c.1516 C>T mutation. The DNA sample of II:3 is not available in Pedigree 3.
- (B) Audiograms of three probands showing bilateral severe sensorineural hearing loss. The blue curves indicate the left ear and red curves indicate the right ear.
- (C) High-resolution radiology results using computed tomography (CT) or magnetic resonance imaging (MRI) show normal inner ear development indicated by white arrows. Note: Due to infection of the first cochlear implant, the proband of Pedigree 2 received a second cochlear implant operation. The CT image shown here was obtained prior to implantation of the second cochlear implant. The implanted cochlea is indicated by the blue arrow.
- (D) Pictures of the hands show the absence of the fifth finger and thumb nails indicated by black arrows, fifth finger phalanx deficiency indicated by white arrows, as well as onychodystrophy-like malacia and pitting of the middle three fingernails.
- (E) X-ray of the hand shows fifth finger phalanx deficiency indicated by white arrows.
- (F) Pictures of the feet show the absence of all toenails.
- (G) X-ray of the foot shows no abnormalities.

Figure 1. Phenotype of the three Chinese DDOD (dominant deafness-onychodystrophy) probands.

Evidence Support that a De Novo Mutation in ATP6V1B2 Causes the DDOD Syndrome

Blood samples (~3-5 ml) were drawn from 6 participants so that genomic DNA could be extracted with the Genomic DNA isolation kit (QIAGEN). Paternity was confirmed by genotype analysis of 19 informative short tandem repeats (STRs) using Goldeneye™ 20A kit (Peoplespot, Beijing, China) [11], yielding a probability of paternity of 0.999999 (assuming a prior probability of 0.50). Exome capture was performed in pedigrees 1 and 2, including the two probands and their parents, by BGI–Shenzhen using NimbleGen SeqCap EZ Human Exome Library v2.0 (Roche NimbleGen, Inc., Madison, WI, USA) according to the manufacturer’s protocols, and sequencing was performed using a HiSeq2000 platform (Illumina, San Diego, CA, USA). Illumina base calling Software 1.7 was used with default parameters to process the raw image files and to sequence the individual products as 90-bp paired-end reads. The sequenced reads were aligned to the human genome reference (UCSC hg19 version, build37.1) using SOAP aligner/SOAP2 [12]. SNP or indels were called using Soapseq [13] software and bwa [14], respectively. The alignment results were identified using GATK [15] to identify the breakpoints.

Table 1. Filtering of SNP variants obtained in whole exome NGS[9]

SNP Filter process	Individual 1	Individual 2
Total	110722	117704
Functional	14472	14642
Filtered_1000Genomes	2491	2545
Filtered_1000Genomes_Hapmap	2469	2521
Filtered_1000Genomes_Hapmap_EVS	2469	2521
Filtered_1000Genomes_Hapmap_EVS_control	215	242
Filtered_1000Genomes_Hapmap_EVS_control_BGI	83	96
Genes shared by individual 1 and individual 2	6*	

* Details were shown in Table 2.

In each sample, we obtained approximately 5.9–6.9 Gb of data after whole exome sequencing. The data mapped to the targeted region have a mean depth of 145.74 folds, and 99.41% of the targeted bases was covered. For bioinformatic analysis, we focused on variants in coding regions. Variants in individuals and their parents were filtered by four databases, including the 1000 Genomes Project, HapMap database, the EVS database, and in-house database from the BGI, with the Minor Allele Frequency lower than 0.005. Based on 1) the dominant inheritance of DDOD, 2) the identical phenotype of the two probands, and 3) the pedigree traits (only one individual and neither parent had symptoms) based on the assumption that there may be a de novo mutation following the dominant inheritance characteristics. Under assumptions of the autosomal-dominant analysis strategy (when incomplete penetrance can be excluded), the case must have a heterozygous mutation in a certain gene, while the control has no mutation. After completing such a filtering process, we identified 6 genes with variants shared by the two individuals (Table 1). Detailed variants in the six shared genes can be found in Table 2. Among the six genes, no known hearing-loss-related gene was identified. The 14 variants in the six shared genes were then tested by

Sanger sequencing. Considering the sequencing results, the prediction results by SIFT, Polyphen, Mutationtaster, the genes' pathway and their expressions in human fetal cochlear ESTs database, *ATP6V1B2* was identified as the gene associated with DDOD. An identical heterozygous missense mutation (c.1516 C>T [p.Arg506X]) in *ATP6V1B2* was verified in two probands but not in their parents (Figure 2). The above results were further confirmed by Sanger sequencing in another DDOD pedigree (Pedigree 3) we collected in China, in which we found that the proband carried the same *ATP6V1B2* mutation. The *ATP6V1B2* c.1516 C>T (p.Arg506X) mutation segregated with the phenotype within the three DDOD families.

The p.Arg506X in *ATP6V1B2* is a nonsense mutation that inserts a premature stop codon, which results in a truncated protein that lacks the last five amino acids. Conservation analysis of amino acids in nine *ATP6V1B2* orthologs indicated that the last five amino acids (residues 506 to 511) are highly conserved (Figure 2). Three-dimensional protein structure modeling suggested that the p.Arg506X altered structure of *ATP6V1B2*, resulting in a failure of hydrogen bond formation between Tyr 504 and Asp 507 (Figure 3). The absence of this mutation in the parents of the three individuals indicates its *de novo* nature. Using a restriction enzyme (Taq I) assay to perform a molecular epidemiology analysis of the *ATP6V1B2* c.1516 C>T variation in 1053 ethnically matched normal hearing control subjects, we found that none of the normal hearing individuals showed such a mutation (Figure 4). In addition, the c.1516C>T variant is not seen in ESP65000 database.

Immunostaining of mouse cochlea sections and cultured cochlea tissues showed *Atp6v1b2* expression in the organ of Corti, spiral ganglion neurons, the limbus, and fibrocytes close to the stria vascularis (Figure 5). This expression pattern was found in both the early postnatal (postnatal day 2, orP2) and the adult (P30) cochleae.

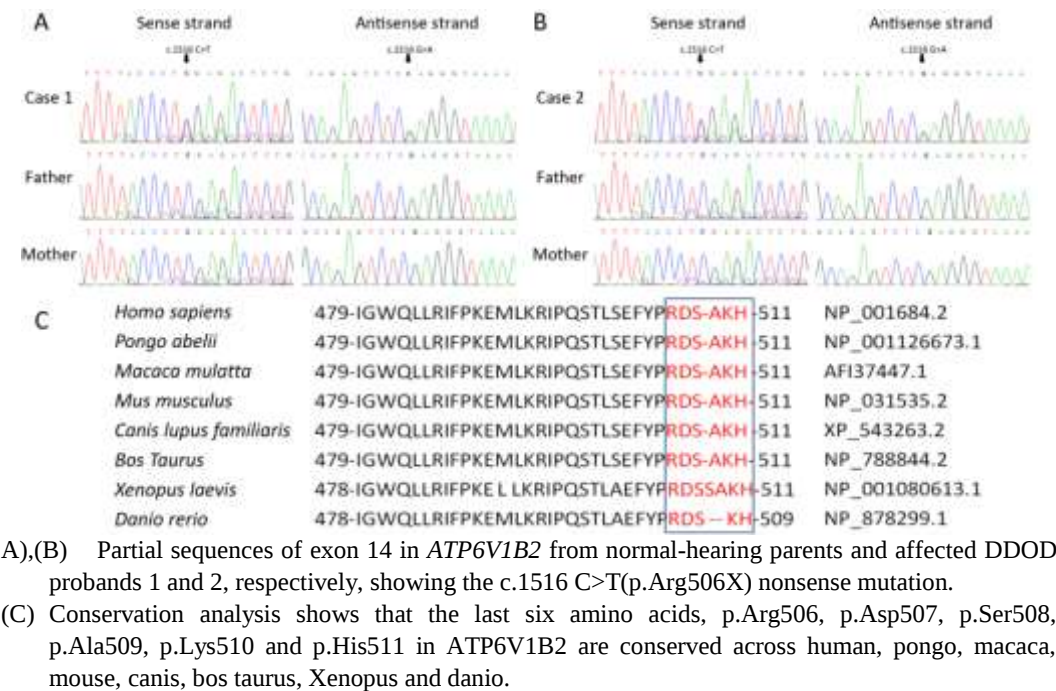
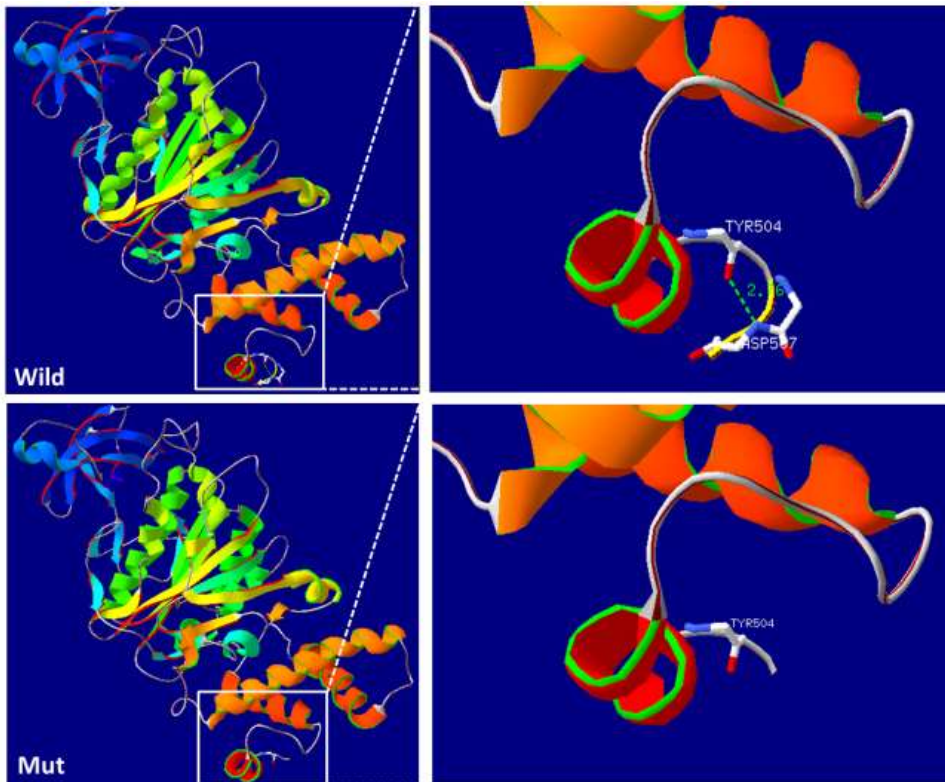


Figure 2. Mutation Analysis of *ATP6V1B2*.

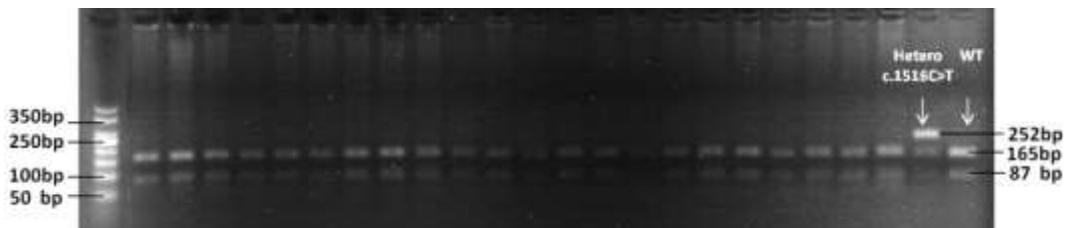
Table 2. Variants in the 6 genes shared by 2 DDOD cases[9]

	Gene Name	Codons	Substitution	Detailed Information for cases	Genotype Quality	Gene description
Case 1	CIB1	-	-	W34A4T3,000, spliceAcceptorSite+6	Low_Confidence	calcium and integrin binding 1 (calmyrin)
	MUC4	CAC11271CAG	H3757Q	S99G123C9,000,missense	High_Confidence	mucin 4, cell surface associated
	MUC4	CCT4703CGT	P1568R	S41G191C7,000,missense	High_Confidence	mucin 4, cell surface associated
	OR5H6	ACT368CTT	T123L	Y97C23T9,000,missense	Low_Confidence	olfactory receptor, family 5, subfamily H, member 6
	PRAMEF1	ATG122AGG	M41R	K20T251G4,000,missense	High_Confidence	-
	AMBN	GGA539GTA	G180V	K43G137T9,000,missense	Low_Confidence	ameloblastin (enamel matrix protein)
	ATP6V1B2	CGA1516TGA	R506*	Y99T56C44,000,nonsense	High_Confidence	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2
Case 2	CIB1	-	-	W32T5A3,000,spliceAcceptor Site+6	Low_Confidence	calcium and integrin binding 1 (calmyrin)
	MUC4	CCT12574TCT	P4192S	R39G140A8,000,missense	High_Confidence	mucin 4, cell surface associated
	MUC4	ACC12568GCC	T4190A	Y45T119C7,000,missense	High_Confidence	mucin 4, cell surface associated
	MUC4	ATG4604ACG	M1535T	R22A54G5,000,missense	High_Confidence	mucin 4, cell surface associated
	OR5H6	GGG239GAG	G80E	R27G216A7,000,missense	High_Confidence	olfactory receptor, family 5, subfamily H, member 6
	PRAMEF1	ATG82GTG	M28V	R35A178G8,000,missense	High_Confidence	-
	AMBN	GGA539GCA	G180A	S22G129C6,000,missense	Low_Confidence	ameloblastin (enamel matrix protein)
	ATP6V1B2	CGA1516TGA	R506*	Y99T61C62,000,nonsense	High_Confidence	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2



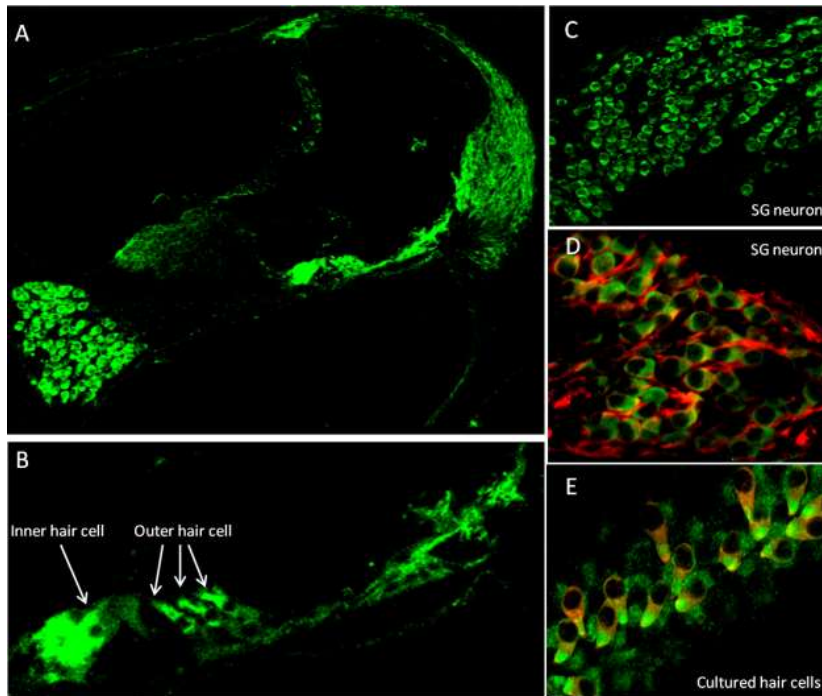
Structure analysis of the wild-type ATP6V1B2 and mutant ATP6V1B2 (by Swiss model Workspace: <http://swissmodel.expasy.org/workspace/>). p.Arg506X results in failure of hydrogen bond formation between Tyr 504 and Asp in ATP6V1B2.

Figure 3. Altered protein structure by *ATP6V1B2* p.Arg506X.



Example gel showing that three bands, 252bp, 165bp and 87bp, in individual with heterozygous *ATP6V1B2* c.1516 C>T mutation, and two bands, 165bp and 87bp, in wild-type controls. The pair of primers used for restriction enzyme reaction was designed around *ATP6V1B2* c.1516 C, which can amplify a fragment of 252bp. The restriction enzyme Taq I recognizes the 'TC' at c.1515 and c.1516. After the Taq I reaction, the 252bp fragment is cut into two fragments of 165 and 87 bp. However, the mutation c.1516 C>T deletes the Taq I restriction endonuclease site. Thus, for the heterozygous c.1516 C>T mutation, three bands (252, 165 and 87 bp) were detected, while in controls lacking the c.1516 C>T mutation, two bands (165 and 87 bp) were detected.

Figure 4. Taq I restriction enzyme assay showing normal versus *ATP6V1B2* c.1516 C>T mutant PCR fragments.

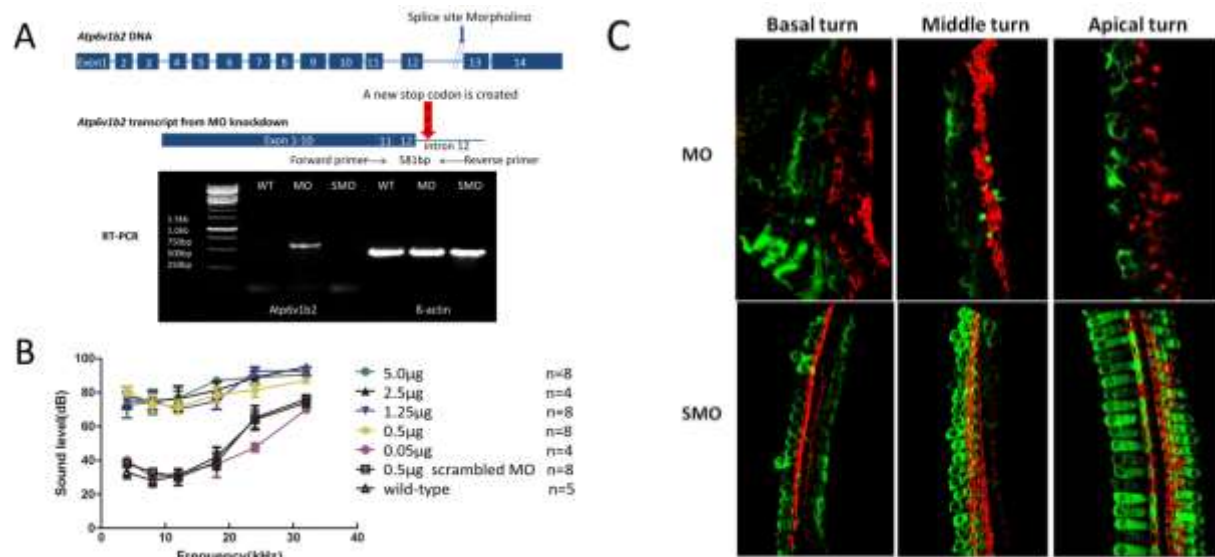


(A) *Atp6v1b2* distribution in mouse cochlea. *Atp6v1b2* expresses mainly in the organ of Corti, spiral ganglion neurons, the limbus, and fibrocytes close to the stria vascularis; (B) *Atp6v1b2* expression in hair cells; (C) *Atp6v1b2* expression in the spiral ganglia (SG) neurons; (D) Double staining of *Atp6v1b2* and tubulin in ganglia neurons. Green: *Atp6v1b2*, Red: β -tubulin; (E) Double staining of *Atp6v1b2* and Myo6 in cultured hair cells. Green: *Atp6v1b2*, Red: Myo6

Figure 5. *Atp6v1b2* expression in the cochlea.

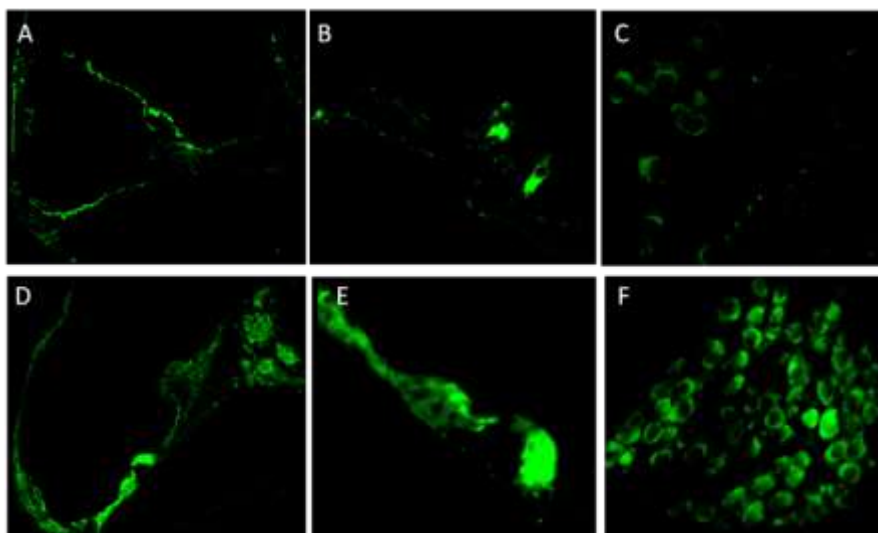
***Atp6v1b2* Cochlea Knockdown Mouse Shows Hearing Loss**

To further investigate the function of *ATP6V1B2* in the cochlea, we generated a mouse model in which the expression of *Atp6v1b2* was specifically reduced in the cochlea using a morpholino oligomer. The oligomer was designed to anneal at the junction of intron 12 and exon 13, which resulted in a partial inclusion of intron 12 followed by a stop codon that excluded the expression of exons 13 and 14 in the mature mRNA (Figure 6A). The *Atp6v1b2* morpholino oligomer was microinjected (0.05–5.0 $\mu\text{g}/\mu\text{L}$) into the scala media of the basal turn of the mouse cochlea before postnatal day three. Hearing sensitivity has been shown to be unaffected by such an injection procedure if the injection was done to mice younger than postnatal day 5 (P5) [16]. Reverse transcription-polymerase chain reaction (RT-PCR) was used to verify the abnormal transcript product containing part of intron 12 in the mouse cochlea 3 days after injection (Figure 6A). At 4 weeks post-injection, auditory brainstem response (ABR) tests measured across a frequency range of 4–32 kHz showed that hearing thresholds in the ear injected with the morpholino oligomer at the concentration of 0.5, 1.25, 2.5 and 5.0 $\mu\text{g}/\mu\text{L}$ were elevated by 30–50 dB compared to wild-type mice. However, hearing thresholds in mice



- (A) RT-PCR analysis shows intron 12 retention in the *Atp6v1b2* transcript of *Atp6v1b2*-specific morpholino oligomer (MO)-knockdown mouse cochlea. The morpholino oligomer was designed to anneal at the junction of intron 12 and exon 13, which resulted in a partial inclusion of intron 12 followed by a stop codon UAA (indicated by the red arrow). The forward RT-PCR primer was in exon 11 and the reverse primer was in intron 12. The RNA was extracted 3 days after morpholino inner ear injection. Since the reverse primer corresponded to intron 12 sequences, it could not bind to the normal *Atp6v1b2* transcript. No bands were observed in the wild-type (WT)- or scrambled morpholino oligomer (SMO)-injected mice. The primer pairs amplified a product of 581 bp, including part of exon 11, exon 12 and part of intron 12 in the presence of abnormal splicing due to the *Atp6v1b2*-specific morpholino.
- (B) Hearing thresholds (y-axis) were determined based on ABR measurements at various frequencies (x-axis) for *Atp6v1b2*-specific morpholino oligomer (MO)-knockdown mice, scrambled morpholino oligomer (SMO) control mice and wild-type mice. ABR thresholds were measured at postnatal day 30 (P30), 4 weeks after cochlea injection. Hearing thresholds in *Atp6v1b2*-knockdown mice at 0.5, 1.25, 2.5 and 5.0 μg/μL were elevated by ~30–50 dB compared with wild-type and scrambled-morpholino-injected mice. Hearing thresholds in *Atp6v1b2*-specific-MO-cochlea-injected mice at 0.05 μg/μL were within the normal range. Legends for different mouse groups are shown in the panel, n= the number of ears. Vertical bars represent standard errors of the mean.
- (C) Flattened whole mount cochlea staining shows the degeneration of hair cells in the *Atp6v1b2*-knockdown mice. At 21 days after cochlea injection with *Atp6v1b2*-specific morpholino oligomer (MO, 0.5 μg), the majority of hair cells in the basal, middle, and apical turns had died. At 21 days after cochlea injection with the scrambled morpholino oligomer (SMO, 0.5 μg), the hair cells in the basal, middle and apical turns remained normal. Green: *Atp6v1b2*; Red: Phalloidin.

Figure 6. *Atp6v1b2*-knockdown analysis in the mouse cochlea.



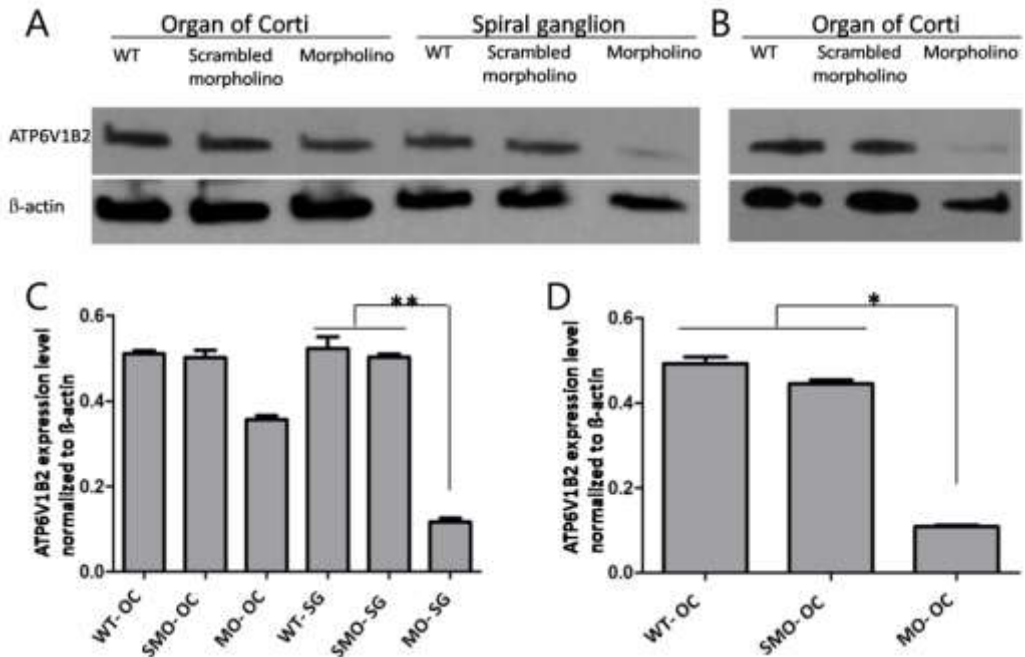
(A) Knockdown of *Atp6v1b2* in the whole cochlea 30 days after cochlea injection with *Atp6v1b2*-specific morpholino (0.5 μ g); (B) Hair cell degeneration 30 days after cochlea injection with *Atp6v1b2*-specific morpholino (0.5 μ g); (C) Spiral ganglia neuron degeneration 30 days after cochlea injection with *Atp6v1b2*-specific morpholino (0.5 μ g); (D) to (F) Whole cochlea, hair cells and spiral ganglia neurons remain normal 30 days after cochlea injection with scrambled morpholino (0.5 μ g). Green: Atp6v1b2

Figure 7. Degeneration of mouse spiral ganglia neurons and organ of Corti in *Atp6v1b2* knockdown mice.

injected with 0.05 μ g/ μ L morpholino oligomer was within the normal range, indicating the dosage dependence of the hearing loss phenotype. In addition, all the mice received scrambled morpholino oligomer (0.5 μ g/ μ L) displayed normal hearing (Figure 6B). These results supported the specific effects of the injected morpholino oligomer. Immunological staining observations revealed that *Atp6v1b2* expression was knocked down significantly in the gross cochlea (Figure 7), especially in the hair cells and the spiral ganglion neurons. In addition, we observed hair cell degeneration in the cochlea that received the morpholino oligomer to knockdown the *Atp6v1b2* expression (Figure 6C).

Western Blot Analysis of *Atp6v1b2* Shows Reduced Expression of *Atp6v1b2* in the Spiral Ganglion Neurons and the Organ of Corti

Western blot analysis performed 7 days after injections demonstrated significantly decreased levels of V-ATPase encoded by *Atp6v1b2* in the group that received morpholino oligomer in both the spiral ganglion neurons (Tukey's multiple comparison test, $P=0.0073$, $q=25.99$) and in the organ of Corti. The comparison was made between the experimental group and the group that received scrambled morpholino oligomer as well as the wild-type group. At three weeks after morpholino oligomer injection, the V-ATPase level was decreased further in the organ of Corti (Tukey's Test, $P=0.039$, $q=10.37$, Figure 8).



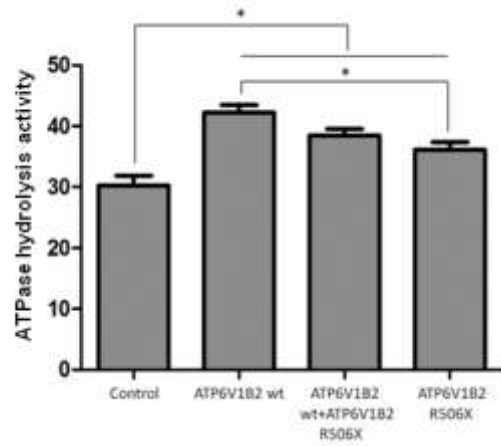
- (A) Western blots of ATP6V1B2 in the organ of Corti (OC) and spiral ganglion (SG) of wild-type (WT), scrambled-morpholino-oligomer (SMO, 0.5 $\mu\text{g}/\mu\text{l}$) control and *Atp6v1b2*-specific morpholino oligomer (MO, 0.5 $\mu\text{g}/\mu\text{l}$)-knockdown mice. Legends for each lane are shown in the figure. Protein was extracted from the postnatal day 9 (P9) mouse cochlea 7 days after inner ear injection.
- (B) Western blots of ATP6V1B2 in the organ of Corti (OC) of wild-type (WT), scrambled-morpholino-oligomer (SMO, 0.5 $\mu\text{g}/\mu\text{l}$) control and *Atp6v1b2*-specific-morpholino-oligomer (MO, 0.5 $\mu\text{g}/\mu\text{l}$)-knockdown mice. Legends for each lane are shown in the figure. Protein was extracted from postnatal day 23 (P23) mouse, 21 days after inner ear injection.
- (C) The band intensities in Figure 8A were normalized to the corresponding β -actin bands for quantification. Two asterisks on top of bars indicate significant reductions in ATP6V1B2 expression compared with the WT and SMO control in the spiral ganglion (Tukey's multiple comparison test, $P < 0.01$). Data are presented as means $\pm$ standard deviation. Four biological replicates are represented in the bar graphs.
- (D) The band intensities in Figure 8B were normalized to the corresponding β -actin bands for quantification. The asterisk on top of the bars indicates significant reductions in ATP6V1B2 protein expression compared with the WT and SMO control in the organ of Corti (Tukey's multiple comparison test, $P < 0.05$). Data are presented as means $\pm$ standard deviation. Four biological replicates are represented in the bar graphs.

Figure 8. Protein levels of ATP6V1B2 in two regions of the cochlea from wild-type, scrambled-morpholino-control and *Atp6v1b2*-knockdown mice.

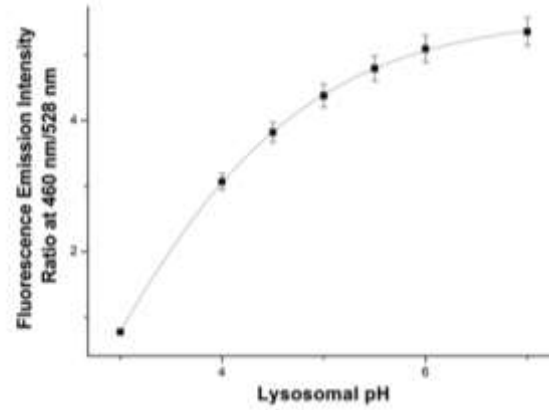
ATP6V1B2 C.1516 C>T is a Dominant Loss-of-Function Mutation, Causing Abnormal Acidification in Lysosomes

To evaluate the pathogenicity of the *ATP6V1B2* c.1516 C>T mutation, we transfected the pIRES2-EGFP-*ATP6V1B2* wild-type plasmid and pIRES2-EGFP-*ATP6V1B2* c.1516 C>T

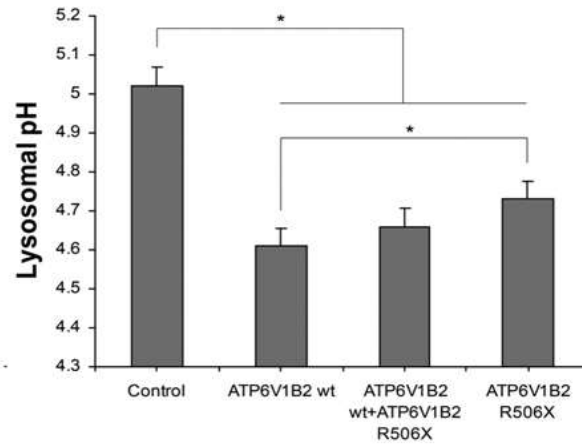
A



B



C



- (A) ATPase assays showed that ATPase hydrolysis activity decreased significantly in the transfected cells as the ratio of the mutant increased. The data in each group represent a sample size (n) of 9. The asterisk on the top of bars indicates a significant increase or reduction in ATPase hydrolysis activity ($P<0.05$), compared to the empty vector control pIRES2-EGFP or pIRES2-EGFP-ATP6V1B2, respectively. Statistical analyses were performed by the Newman-Keuls Multiple Comparison Test. Data are presented as means $\pm$ standard deviation.
- (B) Calibration curve for determining the lysosomal pH in HEK 293 cells. Calibration was performed as described in the Materials and Methods to generate a curve relating to the emission intensity ratio at 460 and 528 nm using an excitation at 360 nm to lysosomal pH. Vertical bars represent standard errors of the mean of four identical samples.
- (C) The lysosomal pH increased in transfected cells as the ratio of the mutant increased, indicating that ATPase proton transport activity decreased as the ratio of the mutant increased. The data in each group represent a sample size (n) of 4. The asterisk on top of bars indicates significant reduction or increase in lysosomal pH ($P<0.05$), compared to the empty vector control pIRES2-EGFP or pIRES2-EGFP-ATP6V1B2, respectively. Statistical analyses were performed using the LSD Test. Data are presented as means $\pm$ standard deviation.

Figure 9. Effects of the ATP6V1B2 ^{p.Arg506X} mutant on ATPase activity in transfected HEK293 cells.

mutant plasmid into HEK293 cells. V-ATPase is expressed in HEK293 cells, and transfection with *ATP6V1B2* caused an overexpression of the V-ATPase. However, no change in *ATP6V1B2* intracellular distribution was detected in c.1516 C>T mutant-transfected cells. We found that the ATPase hydrolysis activity significantly decreased in the transfected cells when the ratio of the mutant increased. The ATPase hydrolysis in cells transfected with *ATP6V1B2* was 42.24 ± 2.11 , that in cells transfected with a 1:1 mixture of *ATP6V1B2* and the c.1516 C>T mutant was 38.48 ± 2.87 , and that in cells transfected with c.1516 C>T mutant was 36.09 ± 2.89 . The ATPase hydrolysis activity in cells transfected with empty vector was 30.28 ± 2.79 (Newman-Keuls Multiple Comparison Test, $P=0.032$, $q=4.508$, Figure 9A). This trends indicated the c.1516 C>T mutant had reduced ATPase hydrolysis compared with the wild-type *ATP6V1B2*.

We measured the proton transport activity of V-ATPase in lysosomes using a lysosome-specific dye. The lysosome pH measurements were 5.02 ± 0.05 in cells transfected with empty vector control, 4.72 ± 0.046 in cells transfected with the c.1516 C>T mutant, 4.65 ± 0.042 in cells transfected with a 1:1 mixture of *ATP6V1B2* and the c.1516 C>T mutant, and 4.59 ± 0.048 in cells transfected with wild-type *ATP6V1B2*. A statistically significant difference in lysosomal pH was detected between *ATP6V1B2* and c.1516 C>T mutant-transfected cells (LSD test, $P=0.02$, Figure 9B and 9C). The ATPase hydrolysis activity and proton transport activity did not differ significantly between HEK293 cells and pIRES2-EGFP-transfected HEK293 cells. These results of the c.1516 C>T mutant that the V-ATPase hydrolysis decreased and the lysosome pH increased which indicated the reduced acidification suggest that *ATP6V1B2* c.1516 C>T is a loss-of-function mutation.

DISCUSSION

Deafness and onychodystrophy diseases (DODs) are classified into two genetically distinct groups: the autosomal recessive form (DOOR syndrome) and the dominant (D) form (DDOD). Clinically, individuals with DOOR syndrome show features such as mild to severe mental retardation, seizures, mutism, hypotonia, congenital sensorineural deafness, triphalangeal thumbs, and hypoplastic nails. The phenotypes of DDOD are milder than those in the recessive form [3], and do not usually involve mental retardation. Features in our DDOD families resembled those reported in several previous studies [4-8] and included deafness, absence of nails and/or toes with more variable presence of brachydactyly, hypoplastic distal phalanges, and bulbous distal phalanges. Of note, the probands reported by Feinmesser and Zelig [8] were affected sisters from a consanguineous family; both had normal intellect, which was suggestive of autosomal recessive inheritance, genetic heterogeneity, or possibly gonadal mosaicism for an autosomal dominant condition. The conditions in the other reported families segregated in an autosomal dominant manner. To date, the hereditary pathogenesis has not been clarified for either DDOD or DOOR syndrome [1], although a neurometabolic etiology has been postulated for latter.

Prior to our study, White and Fahey [5] performed an SNP microarray analysis of one DDOD individual from Australia. However, they found no evidence of a change in copy number. Our study is the first report of a *de novo* heterozygous mutation in the *ATP6V1B2* gene that appeared to be a cause of autosomal DDOD syndrome. The *ATP6V1B2* gene on

chromosome 8p21.3 contains 14 exons and normally encodes 511 amino acids. The availability of two independent individuals with a strikingly similar phenotype was very useful for identifying the causative gene and we took advantage of it. Our results obtained from these two individuals indicated that the *ATP6V1B2* defect causes DDOD syndrome, and this was further verified in a third independent family. The identification of the specific *ATP6V1B2* c.1516 C>T (p.Arg506X) mutation in three independently identified DDOD individuals, but not in a large number (1053 cases) of normal hearing controls, provides further supporting evidence that the p.Arg506X in *ATP6V1B2* is responsible for the DDOD syndrome.

Schinzel-Giedion syndrome (MIM 269150) and Kabuki syndrome (MIM 147920) [17,18] are known to be caused by dominant *de novo* mutations. *De novo* mutations have recently been shown to play a major role in human diseases with reduced reproductive fitness [18-21]. The identification of a same *de novo* dominant mutation in 3 unrelated DDOD individuals by chance should be extremely unlikely. Our results indicate a high correlation between phenotype and genotype in these individuals with the DDOD syndrome. Given a transmission risk of 50% and a recurrence risk of <1% for *de novo* autosomal dominant mutations, compared to a transmission risk of <1% and a recurrence risk of 25% for autosomal recessive inheritance, the relatively high frequency of the *de novo* mutation in our cohort has significant implications for genetic counseling in our individuals and their relatives.

ATP6V1B2 encodes a component of the vacuolar ATPase (V-ATPase, also known as H⁺-ATPase), which is a multisubunit enzyme that mediates acidification of eukaryotic intracellular organelles. V-ATPase-dependent organelle acidification is necessary for intracellular processes such as protein sorting, zymogen activation, receptor-mediated endocytosis, and synaptic vesicle proton gradient generation. V-ATPase is composed of a cytosolic V1 domain and a transmembrane V0 domain. The V1 domain is responsible for ATP hydrolysis, and the V0 domain is responsible for protein translocation. The protein encoded by *ATP6V1B2* is one of the two V1 domain B subunit isoforms, and as it is highly expressed in the organ of cerebrum and in the organelle of *Atp6v1b2*, it is usually called a brain isoform or lysosomal V1 subunit B2 [22,23]. Deficiency in *ATP6V1B2* has been related to hereditary diseases such as osteopetrosis and renal tubular acidosis. It has been suggested that deficiencies of *ATP6V1B1* and *ATP6V0A4* is related to distal renal tubular acidosis and hearing loss [24-27]. To the best of our knowledge, no report has linked the function of *ATP6V1B2* to hearing. The distribution of *Atp6v1b2* in hair cells and spiral ganglia neurons in mouse indicates it may play a role in the auditory system. The gene *related to DOORS syndrome*, *TBC1D24*, encodes a member of the *Tre2-Bub2-Cdc16 (TBC) domain-containing Rab (Ras-related proteins in brain)-specific GTPase-activating proteins, which coordinate Rab proteins and other GTPases for the regulation of membrane trafficking*. *TBC1D24* and *ATP6V1B2* are all known to be widely expressed, most highly in the brain and kidneys. *Tbc1d24* expresses in the stereocilia of the hair cells as well as in the spiral ganglion neurons [28]. *TBC1D24* and *ATP6V1B2*'s identical distribution regions and their function with GTPases or ATPases indicate they may have some physiological link. The hearing loss phenotype of our *Atp6v1b2* cochlea knockdown mouse model confirmed that the normal function of the gene is required for normal hearing. Significantly reduced *Atp6v1b2* expression in the mouse cochlea resulted in the death of hair cells and spiral ganglion neurons, leading to hearing loss.

Cell metabolism depends on the endocytic pathway [29,30]. Lysosomes, the terminal organelles in the endocytic pathway, play an important role in hydrolyzing macromolecules and making their components available as nutrients for the cell. Hydrolytic enzymes in lysosomes are activated by the acidic pH (between 4.5 and 5.0), which is generated and maintained by the activity of the proton-pumping V-ATPase, using metabolic energy in the form of ATP to pump protons into the lysosome lumen [31,32]. Our functional studies demonstrating that the c.1516 C>T mutation caused a decrease in the ATP production and an increase in lysosomal pH indicate that *ATP6V1B2* c.1516C>T is a dominant loss-of-function mutation. According to PhyloP vertebrate conservation scores, the *ATP6V1B2* c.1516 C is a highly conserved base in the genome. The coded amino acid 506 is highly conserved according to multiple sequence alignment and mutant protein structure abnormality predicted by SWISS-MODEL [33]. These support the pathogenicity of the mutation. We propose that insufficient acidification in the lysosome caused by *ATP6V1B2* c.1516 C>T mutation may result in decreased activity of acid-dependent hydrolases, thereby limiting the decomposition of proteins, lipids, and polysaccharides in cells and affecting the development of multiple ectoderm-derived systems. Embryologically, the inner ear, nails, and teeth are all ectoderm-derived organs. The fact that *ATP6V1B2* is ubiquitously expressed in humans makes it reasonable to assume that *ATP6V1B2* may play important roles in other developing ectoderm-derived organs. Knock-in mouse model studies are underway in our laboratory to elucidate the consequences of *ATP6V1B2* mutation on ectoderm-derived organs, with the goal of targeting these effects therapeutically.

In summary, whole-exome sequencing in DDOD pedigrees revealed a *de novo* c.1516 C>T (p.Arg506X) mutation in *ATP6V1B2* that was present in three independently identified individuals with DDOD. Immunolabeling for localization of *ATP6V1B2* in the mouse cochlea as well as functional and morphological studies in the *ATP6V1B2* knockdown mouse model provided further evidences that support the idea that *ATP6V1B2* is a syndromic deafness gene. Direct assessment of the *in vitro* effects of the *ATP6V1B2* c.1516 C>T mutation in transfected cells indicated that it is a dominant haplo-insufficient mutation leading to insufficient acidification of the lysosome. Understanding molecular mechanisms in rare syndromic hearing impairments might lead to valuable insights into the molecular triggers for hair cell and spiral ganglion neuron degeneration and provide the basis for genetic diagnosis as well as new developments in future therapeutic interventions.

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Chapter 25

ASSOCIATION BETWEEN SENSORINEURAL HEARING LOSS AND SLEEP-DISORDERED BREATHING: LITERATURE REVIEW

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ABSTRACT

The cochlea is especially sensitive to circulatory alterations because it is supplied by a single terminal artery and lacks adequate collateral blood supply.

To examine the putative association between Sensorineural Hearing Loss (SNHL) and Sleep Disordered Breathing (SDB) through the literature review is very interesting.

In fact these medical disorders usually are associated to cerebral circulatory alterations resulting in hypoxia, acute hemodynamic change, and decreased cerebral blood flow, because the Sleep Disorder Breathing (SDB), for example OSAHS (Obstructive Sleep Apnea Hypopnea Syndrome), is characterized by periodic hypoxia/reoxygenation. These noxious stimuli can, in turn, activate the sympathetic nervous system, depress parasympathetic activity which results in oxidative stress, endothelial dysfunction, and activation of the inflammatory cascade of different anatomical structure as inner ear. Is reasonable to assume that could cause and/or exacerbate sensorineural hearing loss with/or without tinnitus.

Based on these clinical evidences some authors studied the association between SDB and a dysfunction of auditory pathway showing an improved risk of sensorineural hearing loss, a lower transient otoacoustic emissions (TEOAE) reproducibility and an impairment of auditory brainstem responses in OSAHS populatio. In fact it is known that the transduction mechanism of the inner ear and the transmission of nerve impulses along the auditory way are highly dependent upon the oxygen supply. Recent studies evidenced how through oxidative injury due to a hypoxic stress induced apoptosis in spiral ligament

and in the cochlear basal turn of the Organ of Corti of obese CD/1 mice, causes a high frequency sensorineural hearing loss.

Therefore OSAHS may lead to cerebral vascular insufficiency resulting in hypoxia, acute hemodynamic change, and decreased cerebral blood flow during episodes of apnea with consequent ischemic injury to the cochlea.

Keywords: Sensorineural Hearing Loss (SNHL), Sleep Disordered Breathing (SDB), Hypoxia, OSAHS (Obstructive Sleep Apnea Hypopnea Syndrome), Endothelial dysfunction

INTRODUCTION

Sleep Disordered breathing (SDB), including Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) is a condition, affecting 24% of men and 9% of women in their middle age, associated to high values either of Body Mass Index (BMI) and neck circumference, where intermittent obstruction of the airway during sleep causes sleep fragmentation and repeated desaturations. This disorder carries potentially serious consequences: excessive daytime sleepiness, neurocognitive deterioration, endocrine and metabolic derangements, and is universally recognized as independent risk factor for cardiovascular disease and its related mortality [1-3]. Ear hypoxia is linked to damage of cochlear structures, vascular streaks, afferent synapses, internal ciliated cells but above all it is external ciliated cells of the basal turn which seem most vulnerable: this damage is responsible for sensorineural hearing loss and tinnitus [4-9]. These phenomena lead to a chronic state of oxidative stress resulting in endothelial inflammation, in fact some studies estimated that in patients with sleep-related breathing disorders the probability of a cerebral vascular infarction (CVI) is 3.1 times that in patients without sleep apnea and that 25-50% of all patients who have a stroke suffer from sleep apnea (OSAHS) and have a respiratory disturbance index (RDI) higher than 10. CVI may be caused by variations in intracranial pressure or in intracranial hemodynamics owing to decreasing pO_2 and increasing pCO_2 during cessation of airflow. It is suspected that the most common causes of sudden deafness are vasospasm, thrombosis, embolism, hypercoagulation and sludging [10-15].

Basing on these clinical evidences some authors studied the association between OSAHS and a dysfunction of auditory pathway showing an improved risk of sudden sensorineural hearing loss (SSNHL), a lower transient otoacoustic emissions (TEOAE) reproducibility and an impairment of auditory brainstem responses in OSAHS population [16,17].

WHAT ARE THE MECHANISMS THAT DETERMINE THE AUDIOLOGICAL DAMAGE IN PATIENTS WITH SDB?

The transduction mechanism of the inner ear and the transmission of nerve impulses along the auditory way are highly dependent upon the cochlear oxygen supply,

SDB, in particular OSAHS, is characterised by repetitive airway occlusion resulting in cyclical surges of hypoxia which may occur hundreds of times a night. In addition, OSAHS is

associated with heart failure, stroke and coronary artery disease [18-22]. Endothelial dysfunction, linked to oxidative stress ("Oxidative stress" is the general phenomenon of oxidant exposure and antioxidant depletion, or oxidant-antioxidant balance), a key early event in hypertension and atherosclerosis, has been implicated as a possible mechanism linking the acute cyclical vascular stresses during sleep in OSAHS and the increased prevalence of chronic vascular diseases. Oxidative stress may induce neurotoxicity phenomena that lead to neurodegeneration. As the hair cells of Corti is particularly sensitive to oxidative stress, especially at the mitochondrial level, can go more easily meet degeneration or cell death (disorganization of cochlear homeostasis induced), resulting in an irreversible hearing damage [23]. In addition, the metabolic implications in common with hearing disorders and SDB are obvious, in fact, one of the most important is that anoxia during OSAHS is a potent stimulus for catecholamine secretion and glycogenolysis. An indirect effect regards obesity, as it is tightly connected with diabetes (to emphasize this connection the term "diabesity" has been created) [24,25]. There are also some studies that demonstrate the increase of inflammatory factors in subjects with OSASH: among these, C-reactive protein and cytokines, which are responsible for systemic atherosclerosis and probably have a role in the appearance of neoplasms [26,27] and also evidence of an increase of atherogenic dyslipidaemia [28,29]. Hyperlipidemia determines, at the level of small vessels, a suffering of flow related to increased blood viscosity. This results in a reduced supply of oxygen to the inner ear and its suffering.

LITERATURE REVIEW

Many authors investigated the epidemiologic association between OSAHS and either sudden SNHL and dysfunction of auditory pathway. In a study of Fischer et al. a 7-channel polygraph was used to test 33 subjects with normal hearing and 27 patients suffering from sudden hearing loss and found that 29.6% of the patient group and 21.2% of those in the study control group were suffering from OSA and had RDI >10; this difference was not significant ($p=0.554$). Sudden hearing loss may also be an indicator of arteriosclerosis secondary to such risk factors as hypertension ($p=0.005$), diabetes ($p=0.003$), and hyperlipidemia ($p=0.004$), which were highly significant for the patient group [10]. Sheu et al. evidenced how in a case-control study performed on 19152 patients, OSAHS is present on 1.7% of SSNHL population respect to the 1.2% of the controls with a significant difference between the groups ($P<0.04$) [16]. Recently Casale et al. studied 30 patients divided in two groups, cases (18 subjects) with severe OSA and controls (21 subjects) with snoring without OSAHS and evidenced higher mean values at pure tone audiogram and lower TEOAE signal to noise ratio in severe OSAHS group with significant differences among cases and controls ($P<0.01$) [17]. The authors suggested as possible explanation for the association between SDB and SSNHL, that OSAHS indirectly contributes to the development of SSNHL, the effects of cardiovascular disease and cardiovascular risk factors and that is associated with reduced basal and functional capillarity rarefaction with an additional risk of impaired peripheral perfusion and therefore dysfunction of cochlear hair cells [16,17]. Hwang et al. evidenced how through oxidative injury due to a hypoxic stress induced apoptosis in spiral ligament and in the cochlear basal turn of the Organ of Corti of obese CD/1 mice, causes a

high frequencies sensorineural hearing loss [30]; as also demonstrated by a study of CAO Yongmao et al. which analyzed the hearing at extended high frequencies of patients with obstructive sleep apnea-hyponea syndrome. The youth group, adult group and OSAHS group were tested with pure tone audiometry and high frequency audiometry, and the response ratio was calculated [31]. The conclusion was: the high frequency thresholds increased obviously when OSAHS group comparing with the adult group ($P < 0.01$), and the indicating ratio decreased obviously ($P < 0.05$) [31].

One of the most interesting studies on this topic was conducted by Jau-Jiuan Sheu et al., in this case-control study, identified 3192 patients diagnosed with SSNHL from the Taiwan Longitudinal Health Insurance Database as the study group and randomly extracted the data of 15 960 subjects matched by sex, age and year of first SSNHL diagnosis as controls. Of 19 152 patients, 1.2% had OSA diagnoses prior to the index date; OSA was diagnosed in 1.7% of the SSNHL group and 1.2% of the controls. After adjusting for sociodemographic characteristics and comorbid medical disorders, we found that male patients with SSNHL were more likely to have prior OSA than controls (odds ratio, 1.48; 95% CI, 1.02-2.16) ($P = .04$) [32]. Dziewas et al. in a study performed in 2007 showed how the recurrent intermittent hypoxaemia may be considered a risk factor for peripheral sensory nerve dysfunction and suggested that the treatment for OSAHS might result in an improved function of these nerves [33].

CONCLUSION

The cochlea is especially sensitive to circulatory alterations because it is supplied by a single terminal artery and lacks adequate collateral blood supply [34]. Obstructive sleep apnea may lead to cerebral vascular insufficiency resulting in hypoxia, acute hemodynamic change, and decreased cerebral blood flow during episodes of apnea [2]. In addition, elevated sympathetic nerve activity secondary to the reflex effects of hypoxia and hypercapnia as well as oscillations in blood pressure occurring during episodes of apnea may result in adverse cerebrovascular events and hence ischemic injury to the cochlea [35].

The correlations between SDB and hearing disorders are widely demonstrated in the literature and is still studied.

The presence of sensorineural hearing loss associated with essential hypertension, high cholesterol and high BMI should suspect the presence of SDB misunderstood. This would allow an early diagnosis of these disorders, the resolution of hearing loss and protection to cardiovascular and cerebrovascular accidents.

In fact the early treatment of OSAHS with CPAP (continuous positive airway pressure) improves systemic vascular endothelial function. OSAHS has been implicated in the pathogenesis of hypertension, cardiovascular disease, heart failure, and stroke, all of which are associated with impaired endothelial responses. CPAP treatment may therefore provide an opportunity to reduce the vascular risk attributable to OSAHS, as well as hearing loss, allowing a better and continuous oxygenation of the blood vessels smaller [36].

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Chapter 26

OCCUPATIONAL EXPOSURE TO OTOTOXIC CHEMICALS

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ABSTRACT

There is a growing awareness that a variety of different chemical substances can cause hearing damage in humans. The literature of the last decade on the effect of different chemical compounds on the human auditory system has been reviewed with reference to the exposure in the workplace. Scientific evidence has emerged that the exposure to styrene, p-xylene, solvent mixtures and lead may be a cause of hearing loss. For these substances the number of studies is relatively large and a variety of approaches have been undertaken to test their effect on the auditory system. For other chemical substances, for example certain metals such as mercury, cadmium and arsenic, and some neurotoxic pesticides, the available data indicate a possible ototoxic action, although in some cases only when in combination with noise. A number of critical aspects have been noticed: firstly, this review highlights the need to consider the possible synergistic effect of the interactions between different ototoxic agents, primarily the co-exposure to noise. These interactions are complex and difficult to predict, since synergistic, additive and sub-additive effects have to be contemplated. Then, the individual variability of exposed subjects, due to genetic differences, personal clinical histories, and occupational/environmental exposures cannot be disregarded. Finally, there are conceptual differences among the studies in the definition of hearing loss, which may partly account for the different prevalence values found in the examined documents. In conclusion, it is suggested to adopt the precautionary principle, while awaiting, on one hand, a stronger evidence on the ototoxicity of some classes of chemicals, particularly for exposures at low doses, and, on the other hand, new scientific studies on the effects of the

interaction between physical and chemical agents on the hearing loss that are a priority in future research needs.

INTRODUCTION

The problem of hearing loss, with the consequences resulting from this disease, is of great concern in the medical community. Deafness is one of the most widespread, costly and poorly understood disabilities in the world. According to the World Health Organization (WHO) about 250 million people have disabling hearing loss and two-thirds of them live in the developing world. Millions of people progressively lose their most important means of communication and became socially isolated, especially in the later years of their life (Gatto et al., 2013). Previous studies have shown that hearing deficits can also contribute to occupational injury, although most of these studies evaluated traumatic injury (Hétu et al., 1995; Sprince et al., 2003; Choi et al., 2005). Even if age-related changes, noise exposure and head trauma are the most common causes of damage to cochlear hair cells, several other factors may also cause hearing loss. Since the early 1980s, indeed, some chemical agents have been investigated in order of their potential ototoxic properties in humans. An ototoxic substance is any chemical or mixture that may impair the structures and/or the function of the inner ear (auditory plus vestibular apparatus) and the connected neural pathways; those substances that instead impair hearing and balance by affecting mainly the central or peripheral nervous system are considered neurotoxic. Ototoxic agents are generally divided into two groups, occupational and non-occupational chemicals: this study focused on the first one, even if a brief mention about other xenobiotics that may affect the auditory system is essential. Drugs are considered the main non-occupational substances that may damage hearing: these include, for example, antibiotics, with a place of absolute importance for the aminoglycosides, diuretics, and salicylates, certain antineoplastics such as cisplatin and carboplatin, and anti-malarial medications. In addition, despite the presence of a considerable uncertainty, some lifestyle habits, such as cigarette smoking and alcohol consumption, are also believed to be ototoxic. The classes of compounds discussed in this chapter include organic solvents, metals, pesticides, and other chemicals, including polychlorinated biphenyls and asphyxiants, grouped in a separate class.

ORGANIC SOLVENTS

There is ample scientific evidence that the exposure to several solvents, either alone or in concert with noise exposure, has ototoxic effects. The aromatic solvents of the alkylbenzene family are the largest group among the solvents that have been found to affect the auditory system. Animal models have demonstrated that the relative ototoxicity may vary among the aromatic solvents (Gagnaire & Langlais, 2005). A tentative ranking of increasing ototoxicity for aromatic solvents could be proposed on the basis of cochlea morphological investigation and histological hair cell losses as: α -methylstyrene, trans- β -methylstyrene = toluene $\leq$ p-xylene < n-propylbenzene < styrene = ethylbenzene < allylbenzene. No relationship between the degree of ototoxicity and the lipophilic properties of the ototoxic agents as expressed by the octanol/water partition coefficients was observed. However, correlations between some

structural properties and ototoxicity were observed. A single side-chain on the aromatic ring, except with p-xylene, is essential for ototoxicity. The other aromatic solvents with two side-chains were not ototoxic. When the saturated side-chain was branched (isopropylbenzene, isobutylbenzene, sec-butylbenzene, tert-butylbenzene), no ototoxicity was found. Also the saturation and the number of carbon atoms in the side-chain are of importance. The ototoxic potency increases when the length of the saturated side-chain extended from one carbon atom to two carbon atoms. Of the xylene isomers, p-xylene showed ototoxic effects whereas o-xylene and m-xylene did not (Maguin et al., 2006). Moreover, branching of the unsaturated chain (α -methylstyrene and trans- β -methylstyrene) decreased the ototoxicity of styrene. Finally, some aliphatic solvents, such as n-hexane and n-heptane, as well as trichloroethylene and carbon disulphide, have effects on neurons in the central nervous system, and consequently are supposed to also affect the auditory system (Morata, 1989; Nylén et al., 1994; Simonsen & Lund, 1995; Vyskocil et al., 2008a,b).

Styrene

Styrene is used in the production of plastics, rubber, and resins. Several occupational studies have been investigated the effects of styrene on the auditory system alone or in concert with noise. Reviewed papers were cross-sectional epidemiological studies or occupational health cohort studies. Exposure assessment was based on styrene measurements in the breathing zone, usually also supported by the biological monitoring of its urinary metabolites. In many studies, lifetime exposure to both styrene and noise was calculated using company records and questionnaire data. The results are equivocal. Some studies (Johnson et al., 2006; Mascagni et al., 2007; Morata et al., 2011; Sisto et al., 2013) claimed to have demonstrated styrene-induced hearing loss in industrial populations, also with synergism between styrene and noise, but others (Hoffmann et al., 2006; Triebig et al., 2009) have indicated no ototoxic effects of styrene exposure. Johnson et al. (2006) studied the health effects in 313 workers exposed to noise (> 85 dBA) and styrene and to styrene alone (noise < 85 dBA). Workers exposed to styrene alone or in combination with noise resulted to have significantly poorer pure-tone thresholds in the high-frequency range (3-8 kHz) than the control, noise-only exposed workers and non occupationally noise-exposed. In a smaller study, hearing thresholds of 32 workers in a fiberglass reinforced industry were compared to 60 unexposed control subjects (Mascagni et al., 2007). Twenty-four of the exposed subjects had slightly but significantly higher thresholds at all frequencies (except at 8 kHz on the right ear). The study confirmed the results from earlier studies with larger population that styrene alone can cause a slightly elevated hearing threshold (Muijsers et al., 1988; Morioka et al., 1999; Sliwińska-Kowalska et al., 2003). Similar findings were reported by a large cross-sectional study on styrene-exposed workers from Sweden, Finland, and Poland (Morata et al., 2011). Among the important results obtained from this multicenter study, such as the corroboration of association between styrene exposure and hypoacusis, the authors observed that noise exposure from 80 to 84 dBA did not have a significant effect on hearing, except when in combination with styrene. In a recent study Sisto et al. (2013) evaluated the ototoxic effect of styrene by means of otoacoustic emissions, used as biomarkers of mild cochlear damage. The authors found a significant correlation between the otoacoustic emission levels

and the concentration of the styrene urinary metabolites. Besides, on a subsample of styrene exposed subjects with low exposure to noise and short exposure lifetime, cochlear functionality degradation has been evidenced, manifesting itself with a significant reduction of the otoacoustic signals. In contrast, other studies failed to find any effect of styrene on hearing thresholds. An investigation on 32 workers of a boat building factory found no consistent association and only few isolated correlations between the parameters of hearing acuity and exposure indices (Hoffmann et al., 2006). No clear ototoxic effects were also reported by Triebig et al. (2009). The study examined associations between occupational styrene exposure and impairment of hearing function of a group of workers from a boat building plant. With the exception at frequencies of 1,000 and 1,500 Hz, no dose-response relationship between threshold and exposure data was found. In conclusion, there is some suggestion of a likely ototoxic effect of styrene exposure, but hearing dysfunction deficits, in particular at low concentrations, have not been demonstrated by scientifically reliable argument. Further studies in humans are necessary to clarify this question.

Toluene

Toluene has a number of industrial uses as solvent, carrier, or thinner in the paint, rubber, printing, cosmetic, adhesives and resin industries, as a starting material for the synthesis of other chemicals and as a constituent of fuels. Information gained from animal studies support the observations in humans that toluene can be ototoxic (Pryor & Howd, 1986; Johnson et al., 1988; Sullivan et al., 1989; Li et al., 1992) and demonstrate that toluene exposure can aggravate auditory degeneration in genetically predisposed mice. The data on the ototoxic effect of toluene in humans originate mainly from case reports of acute toluene poisoning. In studies focused on the voluntary inhalation of toluene, severe hearing loss in the central auditory pathways was reported (Ryback, 1992; Morata et al., 1994). Two studies on association between auditory damage and occupational exposure to toluene were identified in the literature of the last 10 years. Chang et al. (2006) described hearing impairment from simultaneous exposure to toluene and noise in 174 workers at an adhesive materials manufacturing plant. Diametrically opposite conclusions have been reached by Schaper et al. (2008). In a five year follow-up study, 333 rotogravure printers exposed to a relatively high level of toluene in the printing area were compared with those exposed to a low level of toluene in the end-processing area. No toluene exposure-related variables (duration, level, urine metabolites) were found to be significant in the logistic regression model. To sum up, toluene may be associated with hearing impairment when the exposure reaches a certain level (Chang et al., 2006); the risk effect may not be observed when the level is lower than 50 ppm (Schaper et al., 2008). However, more studies are needed to confirm these findings.

Xylenes

Xylenes are found in various solvent mixtures, including paints, varnishes, and thinners; they are also used in histology laboratories. Several studies have been compared the ototoxicity of three xylene isomers (Pryor et al., 1987; Cappart et al., 1999, 2000; Campo et

al., 2001; Gagnaire et al., 2001; Maguin et al., 2006). Unlike o-xylene and m-xylene, an ototoxic effect was observed after a sub chronic p-xylene exposure.

In 2008, Draper & Bamiau presented a case-study of a patient with auditory neuropathy after exposure to xylene, and in the absence of any other risk factor. More recently, in a study on a group of 30 medical laboratory workers, Fuente et al. (2013) found significant different ABR latencies for xylene-exposed workers than non-exposed workers.

Dichloromethane

Dichloromethane is a widely used organic solvent in a diverse range of industries such as metals and plastics, electronics, pesticides and textiles. The effects of dichloromethane on the auditory system have been debated in a recent study conducted by Bonfiglioli et al. (2014). The authors reported the case of a transient bilateral hypoacusis after acute exposure to dichloromethane, suggesting a possible ototoxic effect of this solvent.

Trichloroethylene

Trichloroethylene is primarily used as a grease remover, but is also used as a dry-cleaning agent and as a chemical intermediary in the production of paints, waxes, pesticides, and other products, such as adhesive and lubricants.

In animal models, exposure to high concentrations of trichloroethylene has been shown to disrupt cochlear sensory hair and spiral ganglion cells, mainly in the middle turn, as well, i.e., the auditory nervous pathways within the cochlea (Prasher et al., 2004; Albee et al., 2006). In a review of the literature on the effects of low-level exposure to trichloroethylene on the auditory system, Vyskocil et al. (2008b) found no convincing scientific evidence of trichloroethylene-induced hearing losses in workers. No human study on the interaction between occupational trichloroethylene exposure and noise was found.

Carbon Disulphide

Despite the usage of carbon disulfide (CS₂) is strictly controlled by legislation, because of its physico-chemical and toxicological properties, it is still widely used in various sectors such as in the textile industry for the production of rayon fibers and in industrial applications, mainly in tires and other reinforced rubber articles. Carbon disulphide is known to be a neurotoxicant and in some previous studies the effects on the auditory system in workers have been interpreted as a consequence of the known central nervous system (CNS) toxicity of the substance.

Gelbke et al. (2009), in a review of literature on CS₂ health effects, suggest that hearing deficits will only occur at relatively high carbon disulfide exposures, and there may be an interaction between CS₂ exposure and ambient noise levels. The authors concluded that the studies with highest utility support that an Occupational Exposure Limits (OEL) of 10 ppm “may be low enough to protect workers from significant aggravated hearing impairment due to CS₂ exposure in a noisy working condition” (Chang et al., 2003). However, the number of

investigations on electroencephalogram (EEG) alterations and especially on the audio-vestibular system is too small to come to a final decision. Audiometric studies in workers under defined long-term exposure conditions would be helpful in this respect.

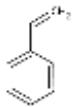
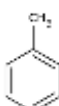
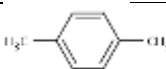
Solvent Mixtures

Several other organic solvents, such as ethylbenzene, n-hexane, methyl ethyl ketone (MEK), ethyl acetate, butyl acetate, have been hypothesized to impair hearing. These chemicals are rarely present separately in workplaces, but mostly as solvent mixtures. Over the recent literature, five occupational studies examining the relationship between solvent mixtures and hearing impairment have been identified. A variety of workplaces was investigated, including paint and lacquer industry, petroleum refineries, aviation industry, shipyards, and work environments exposed to jet fuel. Kim et al., (2005) studied hearing impairments as consequence of simultaneous exposure to noise and mixed solvents in the aviation industry. The major components in the solvent mixtures were methyl ethyl ketone, toluene, xylene, and methyl isobutyl ketone. The study found a prevalence of hearing loss of 54.9% among workers exposed to noise and mixed solvents simultaneously; 17.1% among workers exposed only to noise; 27.8% among workers only exposed to a solvent mixture; and 6% among non-exposed workers. Relative risks were estimated to be 4.3 for the noise-only group, 8.1 for the noise and solvents group, and 2.6 for the solvents mixture group. In a similar study conducted by Kaufman et al. (2005), the exposure to jet fuels, containing several solvents such as n-hexane, n-heptanes, toluene, and xylenes, was found to increase the odds ratio when it is combined with noise exposure during the first twelve years of exposure. The effects of jet fuel exposure on hearing were found statistically non-significant for more than 12 years of combined noise and jet fuel exposure, suggesting a plateau effect for jet fuel exposure and/or that the noise-induced hearing loss may become more important for those continuing to have exposure to both agents. In the last decade two studies on the association between hearing impairment and the exposure to solvent mixtures and noise were published by Sliwinska-Kowalska et al. In the first study (Sliwinska-Kowalska et al., 2004), the authors compared the hearing impairments of 701 dockyard workers (517 noise and organic solvent mixture exposed and 184 noise only exposed) with 205 control subjects not exposed to either noise or solvents. The odds ratio of hearing loss resulted significantly increased by about three times in the noise-only group and by almost five times in the noise and solvent group. In the second study (Sliwinska-Kowalska et al., 2005) hearing disabilities of 1117 workers exposed to both mixtures of solvents (xylene, styrene, n-hexane and toluene) and noise were confronted with 66 workers exposed to noise only and 157 controls. A positive linear relationship was found between exposure to solvents and hearing thresholds at high frequencies. All solvent exposures were found to be associated with hearing impairment, with the lowest odds ratios in the solvent-mixture-exposed group (xylene as the main component), and the highest in the n-hexane and toluene exposed group. The authors also indicated that additional deterioration of hearing at 8 kHz could be caused by co-exposure to solvents and noise. More recently, Fuente et al. (2011) conducted an investigation on central auditory functioning in normal hearing, solvent-exposed subjects (n=46) compared to normal-hearing, non-exposed subjects (n=46). Although all subjects had normal-hearing thresholds, solvent-exposed participants exhibited significantly poorer hearing thresholds in comparison to non-

exposed subjects. Data were in agreement with results from a study conducted in 2007, in which Fuente et al. demonstrated that solvents were significantly associated with poorer pure-tone thresholds, lower amplitudes of transient evoked otoacoustic emissions (TEOAEs), and poorer results for central auditory functioning tests.

In summary, the literature data revealed the increased risk of hearing loss in workers exposed to organic solvent mixture only, and well documented the potentiating of harmful effects of combined exposure to solvents and noise. Hearing impairment is mainly observed in high frequencies, but lower frequencies can also be involved. Some studies have revealed that pure-tone audiometry might be insufficient to differentiate between noise and chemical ototoxic effects (Sliwinska-Kowalska et al., 2004; Fuente et al., 2008, 2011). Finally, it must be emphasized that current exposure limits for solvents, established separately for each single chemical, are probably not effective in hearing protection when they are mixed.

Table 1. Occupational studies on auditory effects of solvents exposure

Substance [CAS]	Structure	ACGIH TLV-TWA (STEL)*	Industrial Uses	Weight of evidence	References
Styrene [100-42-5]		20 (40)	Fiberglass, rubber, plastic, insulation.	O/PO	Johnson et al., 2006; Hoffmann et al., 2006; Mascagni et al., 2007; Triebig et al., 2009; Morata et al., 2011; Sisto et al., 2013
Toluene [108-88-3]		20	Solvent of paints, lacquers, thinners, glues and industrial feedstock	O/PO	Chang et al., 2006; Schaper et al., 2008
p-xylene [106-42-3]		100 (150)	Solvent in leather, rubber and printing industries	O/PO	Draper & Bamioi, 2008; Fuente et al., 2010
Dichloromethane [75-09-2]		50	In paint removers, in manufacturing process of film coatings, as aerosol spray propellant.	NC	Bonfiglioli et al., 2014
Trichloroethylene [79-01-6]		10 (25)	Degreaser in metal industry and in chemical laundries.	NE	Vyskocil et al., 2008
Carbon Disulphide [75-15-0]		1 (3.1)	Man-made cellulosic fibers, tires and other reinforced rubber articles.	PO	Gelbke et al., 2009
Solvent mixtures	Ethylbenzene, n-hexane, carbon disulfide, methyl ethyl ketone (MEK), ethyl acetate, butyl acetate		In dry cleaning, as paint thinners, and glue solvents	O/PO	Sliwinska-Kowalska et al., 2004, 2005; Kaufman et al., 2005; Kim et al., 2005; Fuente et al., 2008, 2011

CAS: Chemical Abstracts Service; TLV: Threshold Limit Value – TWA: time-weighted average; STEL: Short-Term Exposure Limit; O: ototoxic substance, PO: possibly ototoxic substance, NC: nonconclusive, NE: no evidence.

*Values in Parts Per Million (ppm).

METALS

In animal studies, metals such as lead, mercury, cadmium, and manganese are reported to impair inner ear cells, leading to auditory function disorders (Yamamura et al., 1989; Lasky et al., 1995; Ozcaglar et al., 2001; Jones et al., 2008; Kim et al., 2008). Human studies are sparse, but there are some data supporting their effect on auditory system (Chuang et al., 2007; Shargorodsky et al., 2011; Choi et al., 2012; Saunders et al., 2013). The interaction with the noise has been poorly studied either in animals or in humans. Some of the ototoxic metals are discussed in the following section.

Lead

Lead can be found in various workplaces, such as constructions, wholesale trade, industries involved in the manufacture of ammunition, batteries, chemical compounds, explosives, glassware, and metal products. OSHA estimates that approximately 804,000 workers in general industry and an additional 838,000 workers in construction are potentially exposed to lead. Experimental studies on animal models suggest that lead exposure induces degeneration in the inner ear receptor cells and latency in auditory nerve conduction velocity (Yamamura et al., 1989; Lasky et al., 1995). There are contradictory findings on hearing loss from human lead exposure. Several epidemiological studies on lead-exposed workers whose blood lead levels have been related to audiological findings, suggest a probable ototoxic effect for this metal (Chuang et al., 2007; Hwang et al., 2009; Galal et al., 2011). The study conducted by Galal et al. (2011) on a sample of 61 lead-exposed and 50 non-exposed found a significant correlation $r=0.7$ between blood lead levels and binaural hearing impairment. Similar results were observed on 412 workers exposed to low-level lead in a steel plant (Hwang, 2009). In addition of results on lead ototoxicity, Chuang et al., (2007) found that selenium was inversely associated with hearing thresholds, and it may be considered an antagonist to Pb ototoxicity. On the contrary, Counter et al., (2009) were unable to substantiate this in their study on a group of subjects with a history of chronic exposure from occupational Pb glazing. In the past it has also been suggested that lead exposure results in hearing loss may be due to developmental learning disabilities consequent to the exposure to the metal (Schwartz & Otto, 1991; Bellinger, 1995). However, given the current evidence from several human studies, we recommend treating lead as an ototoxic agent.

Mercury (Methyl Mercury Chloride, Mercuric Sulfide)

Occupational exposure to inhaled mercury vapor occurs in many industrial applications, including the production of caustic soda and chlorine, and in the manufacture of thermometers, thermostats, fluorescent light bulbs, batteries, and manometers. Since mercury is known to be neurotoxic, many studies have focused only on the central auditory system, whereas other studies have shown that acute or chronic exposure to mercury generates alterations in both the peripheral and/or central auditory systems (Murata et al., 2004; Rothwell & Boyd, 2008; Prasher, 2009). A recent cross sectional study was carried out by Al-Betanony et al. (2013) on 138 workers and 151 matched controls in a fluorescent lamp factory

in Egypt. The measured noise levels inside the factory were below the maximal permissible limit of the sound intensity inside closed working areas (90 dB according to the Egyptian law). Audiometric air conduction results showed a significantly higher prevalence of hearing loss in the exposed than the comparison group. Other mercury compounds such as dimethyl-mercury, methyl-mercury, and mercuric sulfide have been shown to affect auditory brain stem potentials (Pazderová et al., 1974; Chuu et al., 2001; Clarkson & Magos, 2006).

Cadmium

Industrial use of cadmium mainly occurs in nickel-cadmium batteries, PVC plastics, and paint pigments. Cadmium has a dose-dependent deleterious effect on the auditory system in animal models, causing apoptosis and arrangement alteration of inner ear receptor cells leading to an elevation in auditory thresholds (Ozcaglar et al., 2001; Kim et al., 2008). A probable ototoxic action of cadmium in association with noise exposure was shown by De Abreu & Suzuki (2002), who observed more severe auditory damages, at the frequencies of 4000 and 6000 Hz, in a group of workers exposed to noise and cadmium than in the subjects exposed only to noise.

Chromium

Chromium is used in the manufacturing of stainless steel and to produce several alloys, in plating, corrosion inhibition, wood preservatives, glassware-cleaning solutions, metal finishing and in the production of pigments. In a recent experimental study on animal models, Zhan et al. (2012) found auditory damages with flatness of auditory brain stem responses (ABR) in rats exposed to chromium. Besides, a protective effect of copper and manganese has been supposed, since it has been observed a certain restoration of the hearing function in rats. Regarding human occupational studies, the multiple exposures to a mixture of chromium and lead in combination with noise and their effects on the auditory system were examined by Muttamara & Leong (2004). Elevated concentrations of chromium and lead were found in biological matrices (blood and urine) of exposed workers, as well as high levels of noise, frequently higher than 90 dBA. According to the audiometric test, the workers showed signs of noise-induced hearing loss, but the effect of the co-exposure to the heavy metals cannot be excluded.

Tin

Organic tin compounds are used as heat stabilizers for polyvinyl chloride in piping, siding, and window casings, as antifouling marine paints, wood preservatives fungicides and acaricides. Structural alterations of the auditory system, such as losses or shortening of outer hair cells (OHC) in the basal turn of the cochlea and loss of type 1 spiral ganglion cells, have been reported in animal exposed to trimethyltin (Ruppert et al., 1984; Hoeffding & Fechter, 1991) and triethyltin (Clerici et al., 1993). No study on the effect of occupational exposure to tin compounds on human auditory system has been found in the recent literature.

Arsenic

Arsenic is used in the smelting process of copper, zinc, and lead, as well as in the manufacturing of chemicals and glass. Target organs are: blood, kidneys, and the central nervous, digestive, and skin systems. Animal studies of compounds containing arsenic (sodium arsenilate and its acetylated derivative) have shown histopathological changes in the organ of Corti and the stria vascularis (Anniko, 1976; Miller, 1985). Hearing loss, with particularly marked changes in low-frequency region, has been also reported in human exposed to arsenic pollution (Bencko & Symon, 1977).

To summarize, although some studies show conflicting results, data seem to confirm previous observation of auditory toxicity in workers exposed to lead; and selenium was supposed to reduce its ototoxic effect. Mercury, as well as other compounds containing mercury, affects hearing, with central conduction time delay, but cochlear function may be unaffected. Cadmium causes dose-dependent loss of hearing in animal models; chromium is assumed to worsen the ototoxic action of noise and lead in humans. Studies on arsenic and tin exposures show structural alterations of the auditory system in animal models and low- and high-frequency loss with balance disturbance in humans. Finally, recent studies on cochlear organotypic cultures and animal models (Mao et al., 2011; Apostoli et al., 2013), have confirmed previous findings on the ototoxic properties of other metals, such as manganese and cobalt, which can be also exacerbated by noise exposure.

Table 2. Studies on auditory effects in animals and workers exposed to metals

Substance [CAS]	ACGIH TLV-TWA (STEL)*	Industrial uses	Weight of evidence		References
			Animal models	Human studies	
Lead [7439-92-1]	0.05 mg/m ³	Car batteries, soldering and electrodes in the process of electrolysis, cable covering, plumbing, glazing	O	O/PO	Yamamura et al., 1989; Lasky et al., 1995; Chuang et al., 2007; Hwang, 2009; Galal et al., 2011; Counter et al., 2009
Mercury [7439-97-6]	0.025 mg/m ³	Production of caustic soda and chlorine, manufacture of thermometers, thermostats, fluorescent light bulbs, batteries, and manometers	O	PO	Murata et al., 2004; Rothwell & Boyd, 2008; Prasher, 2009; Al-Betanony et al., 2013
Cadmium [7440-43-9]	0.01 mg/m ³	Nickel-cadmium batteries, PVC plastics, paint pigments	O	PO	Ozcaglar et al., 2001; De Abreu & Suzuki, 2002; Kim et al., 2008
Chromium [7440-47-3]	0.5 mg/m ³	Stainless steel, plating, metal finishing, wood preservative, production of pigments	O/PO	PO	Muttamara & Leong, 2004; Zhan et al., 2012
Tin [7440-31-5]	2 mg/m ³	Stabilizer, antifouling marine plants	PO	NE	Hoeffding & Fechter, 1991; Clerici et al., 1993
Arsenic [7440-38-2]	0.01 mg/m ³	Smelting process, chemicals and glass manufacturing	PO	PO	Anniko, 1976; Miller, 1985

CAS: Chemical Abstracts Service; TLV: Threshold Limit Value – TWA: time-weighted average; STEL: Short-Term Exposure Limit; O: ototoxic substance, PO: possibly ototoxic substance, NC: nonconclusive, NE: no evidence.

PESTICIDES

Several pesticides are expected to be neurotoxic to humans; consequently these compounds may also affect auditory system. In the following section two classes of potential neurotoxic pesticides are evaluated for their effects on auditory system in exposed workers: organophosphates (OPs) and pyrethroids.

Organophosphates (OPs)

OPs represent the largest class of insecticides sold worldwide. Hoshino et al. (2008) studied associations between hearing impairments and chronic exposure to OPs at low doses on a cohort of 18 Brazilian rural workers. Audiometric tests found that 7 exposed (38.8%) had altered results, 4 of them (22.22%) with decreased performances at high frequencies and the remaining 3 subjects (16.67%) with sensorineural hearing loss. Besides, the authors observed associations between time of exposure and test results. The combined effect of noise and OPs on auditory systems was investigated by Guida et al. (2010). Two groups of 40 individuals each, exposed to malathion and noise (group I) and to noise only (group II) were considered. Both groups showed similar hearing loss values in the high frequencies, but at frequencies of 3 kHz (left ear) and 4 KHz (bilaterally) significant differences were found, with a worsening of thresholds for group I. As the more pronounced hearing loss was found in individuals exposed to both elements, it is conceivable a possible interaction between noise and OPs. Similar findings were observed on 43 rural workers exposed to OPs by Camarinha et al. (2011). A high percentage of subjects (83.7%) resulted with worse than expected responses and the results were consistent for all three tests performed – Frequency Pattern Test (FTP), Duration Pattern Test (DPT) and Gaps-in-noise (GIN) test.

Pyrethroids

Pyrethroids are modern insecticides, in most cases more neurotoxic to insects and less neurotoxic to humans than organophosphates. Two types of pyrethroid structures exist: type II contain a cyano-group in the α -position, whereas type I do not contain a cyano-group (Bradberry et al., 2005). Human pyrethroid poisoning is rare, and almost entirely involves type II. The ototoxic effects of the exposure to a mixture containing pyrethroids and OPs have been investigated by a large study among 14,229 subjects (Crawford et al., 2008). The authors found some evidence that pesticide exposures, including poisoning and medical treatment after high exposure events, could increase the incidence of self-reported hearing loss. In particular, the odds ratio for the highest quartile of exposure was 1.19 (95% CI 1.04-1.35) for insecticides and 1.17 (95% CI 1.04-1.35) for OPs. On the contrary, carbamates, organochlorines and pyrethroids resulted not associated with hearing loss.

In two different studies, published in 2000 and 2004 respectively, Beckett et al. obtained conflicting results. In the first study (Beckett et al., 2000) a statistically significant association ($p < 0.05$) was found between hearing loss and pesticide mixture exposure (mainly OPs and pyrethroids) of 185 farm workers. Furthermore, the exposed group presented a higher

incidence (3%) of auditory damages compared to controls. Contrary to these previous findings, the authors found no significant association between pesticide exposure and hearing loss in their further 5-year follow-up study (Beckett et al., 2004). Possible biases, such as the smaller sample size (n=65) than the previous study (n=185), the non-random selection of participating subjects, and the exposure estimation based on recall, might have jeopardized the results of this second survey.

The literature linking pesticide exposure to hearing loss is sparse. Results from recent studies suggest that occupational exposure to some pesticides can induce damage to the central auditory system. Nevertheless, no meaningful conclusions can be drawn, also considering a number of deficiencies of some of the examined studies, such as the lack of detailed information on the level of the exposures. No evidence on the potentiation of noise-induced auditory impairments can be supported. Finally, since many pesticide formulations include solvents, metals, and other so-called inert ingredients, it is possible that these exposures can play a role in the association between hearing loss and pesticide exposure.

OTHER CHEMICALS

There is growing evidence that other chemicals, such as polychlorinated biphenyls (PCBs) and asphyxiants, produce oxidative stress in the cochlea and consequently may have ototoxic potential by themselves and can potentiate noise-induced hearing loss as well (Fechter et al., 2002a,b, 2003; Morata, 2003; Pouyatos et al., 2005, 2007). Occupational exposure to asphyxiant gases is mainly a result of accidental events; therefore, in this section we will analyze the effects on the auditory system of the only carbon monoxide (CO), for which a chronic occupational exposure cannot be excluded.

Table 3. Epidemiological studies on ototoxic action of occupational exposure to pesticides

Pesticide class	Exposed	Controls	Noise	Auditory test	Weight of evidence	Reference
OPs	n = 18	-	NR	Audiometry, VENG, three questionnaires	PO	Hoshino et al., 2008
	n = 40	n = 40	98.5 dB(A)	Audiometry, interview, acoustic-immittance measures	PO	Guida et al., 2010
	n = 48	-	NR	Audiometry, FTP, DPT and GIN, questionnaire	PO	Camarinha et al., 2011
	n = 18	-	NR	Audiometry, VENG, three questionnaires	PO	Hoshino et al., 2008
Pyrethroids and OPs	65	-	76.4÷93dB(A)	Self-reported interview	NE	Beckett et al., 2004
	n = 4926	n = 9303	YES	Self-reported interview	PO	Crawford et al., 2008

n, number of subjects; NR, not reported; VENG, Vector Electronystagmography; FTP, Frequency Pattern Test; DPT, Duration Pattern Test; GIN, Gaps-in-noise; PO: possibly ototoxic substance, NE: no evidence.

Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) consist of 209 synthetic organic compounds, called “congeners,” in which 1 to 10 chlorine atoms are attached to a biphenyl ring. Occupational exposure to PCBs can take place during the renovating and demolishing of buildings, repair and maintenance of PCB transformers, accidents, fires, or spills involving PCB transformers and older computers and instruments, and disposal of PCB materials. Rodent studies provided the first evidence for auditory deficits after developmental PCBs exposure. Perinatal exposure to a commercial PCB mixture, Aroclor 1254 (A1254), resulted in long-lasting low-frequency hearing loss (Goldey et al., 1995). The cochlea was specifically indicated as the likely site of action in a study that found loss of outer hair cells in perinatally PCB-exposed rats (Crofton et al., 2000). The effects of developmental exposure to PCBs on cochlear function seem to be confirmed also by cross-sectional epidemiological studies on children (Longnecker et al., 2004; Trnovec et al., 2008; Newman et al., 2009; Boucher et al., 2010). No current occupational studies were identified.

Carbon Monoxide (CO)

CO is generated by incomplete combustion of any carbon-containing fuel or materials in machines or fire accidents. Occupational exposure to CO, often in combination with noise, notably concerns firemen (Treitman et al., 1980; Lees, 1995; Melius, 2001; Fechter et al., 2002), as well as car mechanics, traffic police and parking lot attendants, bus drivers, truck drivers and taxi drivers (Steenland, 1996; Wickramatillake et al., 1998; Morley et al., 1999; Fechter et al., 2002), motor sport athletes (Walker et al., 2001), service stations workers (Kamei & Yanagisawa, 1997; Herbert et al., 2001), industrial cooks. Studies on animal models have demonstrated the ototoxic action of carbon monoxide and the potentiation of noise-induced hearing loss by CO. The auditory dysfunction produced by carbon monoxide is frequency-specific, as the basal high frequency region of the cochlea is more vulnerable to its effect (Tawackoli et al., 2001). Over the human auditory system, the negative effects of CO exposure have been described mainly after acute exposures to CO (Mehrparvar et al., 2013; Berent et al., 2005; Razzaq et al., 2010). These studies confirm a potential ototoxic action of CO on human auditory system, but did not control or report exposure to noise as a contributor to the observed hearing deficits. The only recent study on the effect of chronic exposure to low level of carbon monoxide in a noisy work environment has been published by Lacerda et al. (2005). The authors analyzed a database with 8647 hearing exams realized by the Quebec National Institute of Public Health between 1983 and 1996. The results demonstrated significant differences ($p < 0.001$) in the auditory thresholds of groups I, composed by subjects exposed to CO and noise (90dBA) and group II, exposed only to noise (90dBA), especially for high frequencies (3, 4 and 6 kHz). These findings in humans and the available evidence on animal models indicate the need for further research on the effects of CO exposure to the auditory system, particularly in populations exposed simultaneously to CO and noise in the workplace (WHO, 1994; Morata et al., 2002).

CONCLUSION

Recent studies have brought attention to the occupational exposure assessment to ototoxic chemicals. Given the growing complexity of the workplace environment, where various ototoxic agents can be simultaneously present, a clear relationship between chemicals and hearing impairment is difficult to assess with epidemiological studies. Quite often, in fact, workers were exposed to various substances that can interact in a synergistic, additive and sub-additive way, highlighting the need to develop further studies, which can provide a better understanding of the dose-effect relationship. The findings over the literature of the last decade suggest that chemicals such as solvents, metals and pesticides may have ototoxic properties. In particular, human studies in workers exposed to solvents including styrene, toluene, p-xylene, have shown a higher prevalence of hearing loss among solvent-exposed workers when compared with unexposed controls. It is a concern that, in some studies, increased risk of hearing loss was found at exposure concentrations of toluene and styrene lower than the recommended exposure limits. Furthermore, studies carried out in both animal models and human subjects exposed to metals, such as lead, mercury, chromium and cadmium, indicate that these chemicals may result in auditory dysfunction. There are indications that also other organic pollutants, such as pesticides and PCBs, are associated with poorer hearing thresholds of the exposed population, which consists not only of workers but also of particularly vulnerable subjects, such as children and pregnant women.

A concomitant agent very often present in many workplaces is noise exposure. Epidemiological studies report conflicting data, but in some cases indicate a conceivable interaction between chemicals and noise, at least for high exposure levels. No meaningful conclusions, however, can be drawn, also considering a number of uncertainties of these studies, including the lack of detailed information on levels and modalities of the exposure and the deficiency of comparable exposure between groups. Furthermore, in most of these studies, the chronic effects were related to chemical concentrations and noise levels measured at the time of the study, which in some cases could result different than those ascertained in past years. While awaiting more evidence for dose-response assessments, for precautionary action, work exposure standards cannot rule out a likely relationship between solvent exposure and hearing impairments. In conclusion, it is believed useful to report the following recommendations as a general guideline for industrial hygienists:

- Risk management measures aimed at reducing exposure to ototoxic substances should be encouraged.
- For workers co-exposed to noise and ototoxic substances a more frequent health surveillance should be considered, regardless of the level of exposure to noise.
- Appropriate tools should be developed for early diagnosis of chemically induced hearing impairment. Otoacoustic emissions tests could be a valuable complement to pure tone audiometry.
- In workplaces characterized by simultaneous exposure to noise and ototoxic substances, on the basis of the precautionary principle, the use of personal protective equipment by the noise from exposure levels greater than 80 dB (A) should be recommended.

- Finally, training and information of workers should highlight the risk of possible synergistic effect of exposure to chemicals ototoxic and noise.

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Chapter 27

CONDUCT DISORDER IN CHILDREN AND YOUTH WITH HEARING IMPAIRMENT

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ABSTRACT

Hearing impairment is a condition that involves medical, psychological and social aspects. Surveys report that children and adolescents with hearing impairment show high prevalence of psychopathology. Among numerous definitions which are largely overlapping (Oppositional Defiant Disorders, Externalizing Disorder, Behavior Problems, Socio-emotional Problems), we have chosen the definition of conduct disorder given by the World Health Organization in ICD -10. Some of the criteria for the diagnosis are: violation of the rules of adults, frequent anger and resentment, deliberate destruction of other people's property. The aim of this paper is to examine the relationships between hearing impairment and conduct disorder. The survey was conducted in Serbia, the environment characterized by specific circumstances concerning the educational and socio-economic conditions. This society has not developed a tradition of inclusive education for children, and inclusive trends are slow in general. The study was conducted on 375 patients of whom 169 are with a hearing impairment, and 178 with no hearing impairment. The respondents with hearing impairment attended school for hearing-impaired children. Some of the respondents with hearing impairment live in abroad school and some with their families. As an instrument, we used a scale for assessing behavioral disorders (Dimoski, 2004), which was filled by the specialists working in the institutions for children and youth with hearing impairments. The survey did not show statistically significant differences in the presence of behavioral disorders in the sample without hearing impairment and the sample of individuals with hearing impairment. However, the results showed that the children with hearing impairment showed significantly greater degree of two indicators of behavioral disorders - the tendency to steal ($t = -3.18$, $p = 0.002$) and extortion of money or benefit from the younger or weaker ($t = -2.07$, $p = 0.039$). This paper also deals with correlates of behavioral disorders in all

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patients (sex, age, academic achievement, socio-economic status) and with connection to the onset, severity of hearing impairment and type of accommodation (boarding or family) in the group of patients with hearing impairment. The male respondents ($t = 3.07$, $p = 0.003$) with lower school achievement ($F = 11.219$, $p = 0.000$) have more evident indicators of behavioral disorders. This work has important implications relating to the practice of working with children and youth with hearing impairment. It was recommended to work on prevention of behavioral disorders, and suggested which types of psychosocial interventions for those who express this disorder may be used.

Keywords: hearing impairment, conduct disorder, children, youth, practice of working

CONDUCT DISORDER IN CHILDREN AND YOUTH WITH HEARING IMPAIRMENT

Problematic behavior in children and adolescents is a common subject of studies in contemporary researches. It is approached to these researches from the perspective of psychology, psychiatry, pedagogy and other related scientific fields. The research of problematic behavior in children and adolescents is followed by methodological difficulties related to the lack of precise terminology used to determine the object of study, and various criteria by which certain manifestations of behavior are treated as problematic behavior in children and adolescents. The large number of various definitions, which are often at least partially overlapping is used. The terms: antisocial behavior, externalized behavioral problems, oppositional defiant disorder, behavioral problems, socio-emotional problems, conduct disorder, and specific criteria that define this phenomenon were used. In Serbian language the terms that are in common use are: juvenile offenders and delinquents. There are also various categorical and dimensional approaches to the definition of these phenomena.

The approaches of the researchers are not in compliance neither. Some senior researchers support the attitude that antisocial behavior in childhood and adolescents is a unique syndrome, regardless of variety of symptoms relating to the phenomenon (Robins, 1966, Robins & Ratcliff, 1980) while many recent studies, as well as factor analysis do not confirm this hypothesis. Summing up the results of the factor analysis of a large number of different studies, it was concluded that the problematic behavior of children can best be conceptualized on the basis of two dimensions, namely discovered-hidden dimensions and destructive-non-destructive dimension (Frick et al., 1993).

In *Diagnostic and Statistical Manual* (DSM-IV) conduct disorder is related to the repeated and persistent patterns of behavior that violates the basic rights of others and the general norms and rules appropriate to age (aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules).

In modern dimensional systems the division of the externalized and internalized behavior problems is accepted (Achenbach & Rescorla, 2001). We have isolated two externalized syndrome, which are only partially consistent with the diagnosis of DSM-IV. The first syndrome, called aggressive behavior, includes oppositional defiant behavior and aggressive conduct disorder, while other syndrome, so-called behavior that violates the rules, includes only non-aggressive forms of behavior disorders. This division implies the existence of two types of behavioral disorders. The first “discovered” or “aggressive” type, characterized by

hostile confrontations with others, either in the form of a legal opposition or aggressive behavior, and other “hidden” or “non-aggressive” type includes symptoms of conduct disorder, which does not includes a confrontation with the victim, substance abuse and association with delinquent peers (Loeber & Schmaling, 1985).

We have accepted the definition of conduct disorder offered by the World Health Organization ICD-10, 1993. In the scientific and professional practice in Serbia none of the definitions is unanimously accepted. Determination of the ICD-10 is largely used in clinical work with children and young people with this kind of disorder which led us to choose this definition. Some of the criteria for the diagnosis of conduct disorder are: often reluctance or refusal of requests and rules of adults, deliberately destroying other people's property, sensitivity and tendency to be annoyed by others (*Often touchy or easily annoyed by others*), frequent anger and resentment (*Often angry or resentful*) excessive fighting with other children, excluding children in the family (*Excessive fighting with other children, with frequent initiation of fights (not including fights with siblings)*), criminogenic episodes involving confrontation with the victim - intimidation, extortion, frequent truancy from school beginning before 13 years of age. It is considered that it is more significant for the foresight to take into account the severity and not the exact type of symptoms. During diagnosis, manifestations of behavioral disorders that last no less than six months and are not isolated antisocial acts are taken into account. This classification makes a distinction between socialized, none-socialized and oppositional defiant disorder.

The existence of different approaches in diagnosing the problematic behavior in childhood is a major reason for the inconsistency of the data on their prevalence. In a study in which the criteria of the DSM are applied, the prevalence of conduct disorder among children and adolescents ranges from 1% to 9%, while the opposition defiant disorder is not so present, with prevalence of about 2% (Essau, 2003). Frequency of externalized problems in the total population of children and adolescents ranges between 2% and 15% (Hinshaw, 1992). Conduct disorder, which involves persistent patterns of rule-breaking and violent behavior, is estimated to have a prevalence of 9% for boys and 2% for girls (Offord et al, 1986). In Serbia, the research Zunic-Pavlovic et al, (2009) shows that 12% of students exhibited antisocial behavior, and in 6% of the deficit of social competence and antisocial behavior is present.

The presence of psychopathology during developmental period in children and adolescents with hearing impairment is a frequent subject of study. Also, the presence of behavioral problems of children and youth with hearing impairments has been studied, although in this area there are several approaches of the authors and defining disorder. However, the development of research dealing with the presence of specific behavioral disorders in children and adolescents in this population is absent.

Imprecise terminology and a variety of criteria for diagnosis are followed by specific methodological difficulties related to the procedures and instruments by which we determine the presence of problem behavior in children and young people with hearing impairment. Assessment of children is difficult, due to the inability of deaf children to understand verbal instructions or verbal tasks placed before them, and the limited expressive aspects of language and speech. Experts generally do not have enough experience or social skills to conduct diagnostic assessments and are not familiar with sign language. Sometimes they include sign language interpreters, whose presence necessarily affects the tested situation. The presence of behavioral disorders is generally assessed based on the reports of parents and teachers, and

some research suggests peer evaluation about the functioning of a particular child in the school context. However, estimates of the parents must not be objective, and are often saturated by subjective interpretations of children's behavior. Some authors (Van Gent, 2007) believe that the most reliable are the estimates of experts. In addition, certain symptoms (especially those related to internalized problems) have distinct subjective tone and are best detected on the basis of introspection.

In Serbia, the studying of children and youth with impaired hearing by psychologically measuring instruments is accompanied by the difficulties related to the lack of a standardized sign language in which it would be possible to translate the items of the instrument, as well as a shortage of professionals who are trained in the diagnosis of psychopathology, developmental age of this specific population. Families and children and youth with hearing impairments use the expression of spontaneous gestural communication to achieve communication. Schools and medical facilities for persons with impaired hearing have no systematized praxis on the field of communication using the sign language.

Contemporary research practice is followed by attitude that different variables, which are often not sufficiently controlled in research studies of personality of children and youth with hearing impairments (speech development, the degree of experiential, emotional, social and educational deprivation, etiology and time of occurrence of hearing loss, the time of initiation and duration of rehabilitation, the existence of cochlear implants, etc.) strongly influence the results of this group of people on personality tests. This situation is particularly applicable to the assessment of the developmental period of psychopathology, including the presence of a behavioral disorder. In studies dealing with psychopathology developmental age of children and youth with hearing loss in our society, the control of the relevant variables often lack. This particularly concerns the variables related to socio-emotional deprivation of children and youth with hearing impairments characteristics of dynamics of family relationships and the conditions of education and rehabilitation.

In Serbia, the children and young people with hearing impairment attend almost exclusively special schools for education of this population and a large number of them is housed in dormitories, or are separated from their families, already at the preschool level. A significant percentage of children and youth with hearing impairments who are educated in this system of special education have not enough well-developed language and speech abilities. The percentage of children with cochlear implants is negligible.

The importance of language and verbal abilities for adequate development many studies have emphasized. Quirin & Lane (2012) show that poor language skills can cause difficulties in understanding the social environment and, in turn, are related to an impaired emotion understanding. Many studies suggest that a delay in language development of children and youth with hearing impairment is in connection with serious difficulties in developing a proper understanding of emotion (Rieff & Terwogt 2006; Meerum Terwogt & Rieff, 2004). Some studies (Dammayer, 2009) even show that good oral or sign communication with the environment is in relation to the normal prevalence of psychosocial problems in deaf children and youth.

These difficulties may explain that the prevalence rates of mental disorders in hearing-impaired children and adolescents found in the literature vary from 15% to 60% (Bailly et al., 2003). Some studies provide disturbing data on the prevalence of psychiatric disorders in young people with hearing impairment. Hindly (1994) provides information about more than 50% of children between 11 and 16 years, Colvin et al. (1979) cites 54%. Van Gent et al,

(2007) provide a comprehensive overview of recent studies of psychopathology in children and adolescents with hearing impairment analysis instruments for the evaluation. Their research indicates elevated levels of psychopathology. However, some studies do not confirm a difference in the manifestation of symptoms of psychopathology in a population of deaf and hearing respondents. Sinnkoeen (1994) confirmed the slightly higher incidence of psychopathology in young people with hearing impairment, but this difference was not statistically significant.

Hearing impairment among children affects psychosocial development, but there is no consensus about the rate of prevalence. Older studies (Meadow, 1980, Freeman et al, 1975) suggest prevalence of 8-23% presence of socio-emotional problems. The largest number of recent studies (Vostanis et al, 1997; van Eldik, 1994; van Eldik et al, 2004) confirms these results. Dammajer (2009) states that studies that were performed in the last two decades provide data on the prevalence of psychosocial problems in childhood from 20% to 50%. However, the findings of the authors from Belgium, Maes & Grietens (2004) did not find elevated levels of these disorders in deaf children that were assessed by parents. Bailly et al. (2003) reported that some studies have shown the presence of normal levels of behavior emotional functioning of deaf children and youth.

Older studies (Schlesinger & Meadow, 1971), which gave information about the elevated levels of behavioral problems in this population, were the impetus for further research. Children with hearing loss have a higher level of externalized behavioral problems (30-38% van Eldik; Vostanis, et al., 1997) than children with normal hearing. Mitchell & Quittner (1996) reported that half or one-third of children and adolescents with hearing impairment (depending on whether they are evaluated by parents or teachers) exhibit behavior problems. Regarding behavioral disorder studies indicate the presence of a 12% and 14% of children and adolescents with hearing impairment compared to 7% in the control group (Hintermair, 2007). Expert's estimates show the presence of behavioral disorders in 11% of children and youth with hearing impairments (Van Gent, 2007).

Complex relations between neurological, family and social factors are basis of conduct disorders in children and adolescents with hearing impairment (Meadow, 1980). Theoretical perspectives on this issue are related to assumptions about the specific environmental conditions of children with hearing impairments which affect their emotional development or lead to the manifestation of behavioral problems. Family environment, in this respect, has a very important role. Difficulty in verbal communication and gestures between parents and hearing impaired children strongly influence the overall development of children, not just the transfer of information. Conditions of wider social environment are related to environmental factors, the socio-economic, through general social factors, conditions, rehabilitation and education, and especially terms of social acceptance of people with hearing impairment, contributes to the development or maintenance of various psychopathological symptoms.

Attempts to understand the development of conduct disorder in contemporary literature range from taking into account the role of genetic and biological predisposition over the characteristics of temperament, socio-cultural context, family relationships, experience rejection by peers, social-cognitive factors etc.

Contemporary concepts are characterized by eclectic approach to the authors and involve the effects of multiple factors in the development of the disorder and emphasize the need for verification of theoretical concepts in empirical research. Many models are a synthesis of different theoretical approaches and research findings (Moffitt, 1993; Patterson & Yoerger,

1997; Lahey & Waldman, 2002, Dodge and Pettit, 2003; Frick and Morris, 2004). Dodge & Pettit (2003) offered a bio-psychosocial model of the development of chronic conduct problems. This model posits that biological dispositions and sociocultural contexts place certain children at risk in early life but that life experiences with parents, peers, and social institutions increment and mediate this risk. They point out that certain types of mutual influences that occur between predispositions, context and life experiences of the child or adolescent, may contribute to the occurrence of behavioral disorders. In the process of developing this disorder cognitive and emotional processes play the role of mediator.

The nature of conduct disorders, as defined by ICD-10 criteria is related to the expression of resistance and aggressiveness towards the environment (peers, adults, things, institutions, rules, etc.). We believe that we should take into account the hypothesis on the tendency of children and youth with hearing loss to a more distinct expression of aggression through such nonverbal (behavioral) ways, rather than through verbal, which are not sufficiently developed for this population. The expression of emotions, including aggression in children and adolescents with hearing impairment is different than the normal hearing children and youth. As stated Rieff et al. (2003) recent findings have shown that deaf children have a different rationale for the emergence of emotions than their hearing peers. They have restricted opportunities to learn from their own and others' experiences in this respect. The research of Reiff & Terwogt (2006) showed that deaf children employed the communicative function of anger expression differently from hearing children. Whereas hearing children used anger expression to reflect on the anguish that another child caused them, deaf children used it rather bluntly and explained less.

One of the few epidemiological studies of the presence of psychopathology in children and youth impaired in our community (Tadić, 1998) dealt with the presence of behavioral problems. This study demonstrated the presence of lying in 3.2% of subjects with impaired hearing, conflicts with friends in 8% of patients, conflicts with teachers at 3.2%, and the fits of rage, breaking objects and hitting the 8.8% of respondents.

Research are trying to detect variables that may be associated with conduct disorders - gender, age, academic achievement, socio-emotional status, the nature of relationships with peers, especially the experience of rejection by peers, characteristics of temperament, character relationships with parents, the influence of parental styles of parents, presence of criminal and maladjustment behavior in close environment... When it comes to children and youth with hearing impairments in personality tests of the population, usually controlled variables affecting the degree of hearing loss are the occurrence of the hearing loss, rehabilitation characteristics, ways of communication with the environment and especially in the family and etc. We will discuss the variables in more details that are often taken into account in the various studies, which are included in this research.

Surveys consistently show a statistically significant relation between conduct disorder and half of respondents. Boys are more prone to these impairments than girls (Friedrich et al. 1984; Kerr et al. 2004; Björkqvist et al. 1992; Cohen et al. 1993; Crick, 1995; Grotperter & Crick, 1995; Feehan et al., 1994; Offord et al. 1987, Keenan & Loeber, 1994). Peterson (1961) showed that age comparison showed that boys displayed more severe conduct problems than girls at all age levels. From about 4 years of age, boys are more likely than girls to engage in conduct problems (Keenan & Shaw, 1997; Moffitt et al., 2001; Lahey et al., 2000, Tremblay et al., 1996). Lahey et al. (2000) find that the behavioral problems of youth can not be explained without taking into account the gender (and age) differences. These

authors, in a large sample of respondents aged 9 to 17 years found that boys were more likely to express aggression, and to have a common property, and misdemeanor offenses. Instead of physical aggression, females tend to use indirect, verbal and relational aggression. Moffit et al. (2001) present new findings on a number of subjects of both sexes from 3 to 21 years aligning approaches of developmental psychology, psychiatry and criminology. They suggest the need for revision of the diagnostic criteria of conduct disorder suitable for girls. Study Keenan et al. (1999) report on studies of behavioral disorders limitation only regarding boys. They believe that understanding gender differences in the course and severity of conduct disorder may lead to important information about etiology.

Research findings on the relation of conduct disorders and academic achievement are consistent, and an interest in author large. Children and adolescents of lower academic achievement are more likely to express behavioral disorder than those of academic achievement. Antisocial behavior is treated as a variable that has a negative impact on academic achievement throughout the years of educating (Bardone et al., 1996; Stott, 1981, Hawkins et al., 2003, Masten et al., 1995; Williams & McGee, 1994). Research (Dodge & Pettit, 2003; Hinshaw, 1992; Maguin & Loeber, 1996; Hinshaw & Anderson, 1996) show that externalized behavioral problems (externalizing behavior) are quite stable in early childhood, the relationship between antisocial behavior and academic skills may establish more in pre-school period and in the later period, this relationship becomes more apparent.

The researchers' interest was stimulated by the fact that the existence of behavioral problems of children with poor school achievement represents an impairment which required professional intervention. But the presence of lower academic achievement phenomenon can not be seen only in the educational context, since it can lead to self-esteem deficits and interpersonal difficulties (Mann & Brady, 1988; Lagreca & Stone, 1990).

Also, the common occurrence of behavioral disorders and poor academic achievement may be treated as a clear predictor of later lack of adaptation in adolescence, which can lead to antisocial behavior and substance abuse (Hinshaw, 1992). Vostanis et al. (1997) found that poor functioning in school variable best predicts the presence of behavioral and emotional problems in children and adolescents with hearing impairment. Many authors (Williams & McGree, 1994) pointed out the importance of reading skills in commonly injured children and youth with hearing impairments and their relationship with challenging behavior.

Developed research practice concerns the attempts to determine the relationships between risk factors of the environment and the occurrence of antisocial behavior. Environmental effects, those related to family and related to the environment, highly correlate (Ingoldsby & Shaw, 2002; Leventhal & Brooks-Gunn, 2000), although it is considered useful to separate them for a deeper understanding of the etiology (Schonberg & Shaw, 2007). From about five to six years of age, differences in conduct problems in children living in disadvantaged neighborhoods become more pronounced even after controlling family demographic characteristics (Brooks-Gunn, Duncan, Klebanov & Sealand, 1993; Chase-Landsdale & Gordon, 1996). Research findings (Lahey et al., 1999, Sampson et al., 1997), generally suggest that children and adolescents from families of lower socioeconomic status are more likely to express behavioral disorder than those from the upper. Keenan et al. (1997) have given the finding that child from low-income families in nearly 5% of express behavior disorder. Research (Hausman & Hammen, 1993; Carr, 1999) indicates the relationship of low socio-economic status, poverty and social isolation and behavioral disorders. Duncan et al.

(1994) find that it seems that the longer the child has been living in poverty within the first four years of life, the more prevalent externalizing behavior problems become.

Many studies confirm that the prevalence of conduct disorder and delinquency is in relation to the different characteristics of the immediate environment (neighborhood), including socioeconomic and cultural conditions of the general (Bursik & Grasmick, 1993; Loeber & Wikstrom, 1993, Sampson & Groves, 1989; Stouthamer- Loeber et al. 1999; Wikstrom, 1991, 1998).

Significant research data (Moffitt et al., 1996; Nagin & Tremblay, 1999) show that nearly half of all children who engage in high levels of conduct problems show considerable improvement by early adolescence. Research suggests that risk factors have a different impact on the occurrence of behavioral disturbances during development and highlights the importance of understanding these complex interactions.

METHOD

Participants

The total sample of this study is $N = 347$ respondents. Part of the sample consists of children and young people with hearing impairment ($N = 169$), or 48.7% of the respondents. They are students of only two special schools for pupils with hearing impairment in Belgrade, capital of Serbia. In these schools the highest percentage of children with hearing impairment are being educated, because in inclusive programs, which are defined by law only in 2013, only small percentage of children and youth is included. The sample did not include the children and young people with hearing impairment who still have some kind of associated disturbances. Regarding the degree of hearing loss, the sample consisted of ($N = 120$) deaf patients, or 71% of the sample ($N = 49$) partially deaf, hard of hearing respondents, or 29% of the sample. Hearing loss is caused by perilingualy $N = 141$, or 83% of the sample, a lingual with $N = 28$ respondents, or 17% of the sample.

Children and youth with hearing impairment attending special schools and living in the dorms, $N = 107$, or 63% of the sample. These are respondents whose families do not live in the Serbian capital (or other cities where there are schools for children and the youth impaired). These children leave the family in the pre-school period and the entire education live in boarding schools. The second part of the sample of children and youth impaired respondents, $N = 62$ who live with their families, the capital of Serbia and attend a special school for the deaf, or 37% of the sample.

The children and youth who were included in the study aged from 7 to 18 years. Included are children of eight years of primary school, and youth first three years of high school. Sample respondents with hearing loss male consisted of $N = 102$ and female $N = 67$.

As an indicator of academic achievement the sample of achievement in school subjects in the previous academic year was taken into account. This variable was divided into three categories: good or underachievement success in school, very good grades in school and excellent school. Success in school subjects with impaired hearing is the largest in the category of great success, 54% of respondents.

Considering the economy, the situation in Serbia and the transition through which the country is going, there are simple difficulties in identifying indicators of socio-economic status of the family, which would be relevant for research purposes. We have opted for the educational attainment of the respondent's father, which is one indicator of the socio-economical position of the family that often accompanies the research in our community. This variable is divided into four categories: elementary school, finished vocational training school, high school and university or university degree. Educational level of the father is in nearly 30% of the sample primary school, or the lowest category of education in Serbia, which implies a low socio-economic position.

The control group consisted of children and young people with a normal hearing ($N = 178$), or 51.3% of the total sample. They are regular students of primary and secondary school in Belgrade. The sample consisted of male respondents $N = 84$, a female $N = 94$. According to school success they were distributed relatively equally in all three categories. Academic success of finished high school of the father of the respondent's is most frequent followed by fathers with secondary education, that is 40% of the sample with proper hearing.

Statistical comparison of groups of patients (with and without hearing loss) showed the following:

1. Group 1 was significantly different from the variable gender ($\chi^2 = 6.041$, $p = 0.005$, Cramer's $V = 0.132$)
2. Groups are significantly different in relation to school success, subjects with impaired hearing have better academic success than subjects without hearing impairment ($\chi^2 = 15.760$, $p = 0.001$, Cramer's $V = 0.213$). Explanation of this difference can be found in a weaker assessment criteria in a special school for deaf students;
3. Groups are significantly different compared to graduates father of respondents ($\chi^2 = 67.132$, $p = 0.001$, Cramer's $V = 0.441$); Respondents with impaired hearing come from lower socioeconomic families compared with patients with normal hearing.

Instrument

In Serbia not one instrument to measure conduct disorders was used in the research practice which is used in Anglo-Saxon scientific research. Also, there are no standardized instruments that are designed for subjects with impaired hearing in this region. Therefore, we decided to use the instrument of the local authors (Dimoski, 2001), *Scale for assessment of the presence of behavioral disorders*. This instrument is filled by teachers of children and youth, the survey respondents. Assessment of teachers matched the plan of this research, given that a large percentage of respondents with impaired hearing lived away from their families, and parents often do not have the relevant data on the investigated phenomena. Some authors (Van Gent, 2007) suggest that the most reliable are the estimates of experts.

The instrument consists of 15 statements that are evaluated on a scale in which 1 point denoted the absence of manifestations of behavior disorder, 2 points, the presence of low intensity, medium presence of 3 points, 4 points expressed presence. The claims set in the instrument are mainly related to the manifestation of conduct disorder as defined in this

disorder ICD-10. The instrument is accompanied by a recommendation from the ICD-10, which suggests that the manifestation of behavioral disorders should be present in the last six months.

Detailed instruction is preceded by the instrument.

Reliability of the instrument, measured by Cronbach's Alpha is 0.921. The reliability of the instrument for sample hearing impaired subjects was 0.934, and the sample of respondents without hearing damage is 0.917.

Procedure

After the detailed planning of the sample, we have started the research. The subjects with hearing impairment were evaluated by their teachers in special schools. Teachers are professionals for hearing impairments (special educators) who are well familiar with the children, at least several years. They are also their homeroom teachers or principal professional persons for training and general care of a particular child.

Subjects without hearing impairment were assessed by their teachers, homeroom teachers in regular education system.

All participants in the study who gave their assessment by filling the Scale of the the presence of conduct disorder were given detailed oral and written instructions. The purpose of the study was explained and their consent to use the results for research purposes was obtained. Previously, the consent of parents of children and youth, and school management was obtained.

RESULTS

The main results of this study concern the estimation of the presence of conduct disorders in hearing impaired children and young people in Serbia.

Table 1. Total score on a scale of conduct disorders in a sample with and without hearing loss

Group	N	AS	SD	T	df	p
No damage	178	21.51	7.02	1.304	262.836	0.193
With hearing damage	169	20.59	5.24			

When used a total score on a scale of conduct disorders it is not possible to determine a statistically significant difference ($p = 0.193$) between patients with and without hearing impairments.

We have accessed to the additional analysis of the items of the instrument in order to supplement the basic findings of research that is not indicating the difference between the two groups in terms of the presence of conduct disorders. For the purpose of the work we have selected items which have statistically significant difference present.

Table 2. T test for items found to have statistically significant differences in the manifestations of conduct disorders in the groups with and without damage

Item	Group	AS	SD	T	df	p
Prone to theft	No damage	1.03	0.15	3.176	208.20	0.002
	With hearing damage	1.53	0.42			
Extort money from younger or weaker students	Without damage	1.02	0.18	2.074	240.55	0.005
	With hearing damage	1.39	0.38			

The research included the identification of correlates of conduct disorders in children and adolescents with hearing impairment. The following are findings that are related to assumed variables that are related to behavioral disorders in children and adolescents with hearing impairment.

Table 3. Summary scores of conduct disorder distributed according to the degree of hearing loss

Degree of hearing impairment	N	AS	SD	T	df	P
Deaf	120	19.63	4.50	-1.518	167	0.131
Hard of hearing	49	20.98	5.48			

Analysis of the total score of conduct disorder shows that in a sample of individuals with hearing loss there were no statistically significant differences ($p = 0.131$) between the deaf and hard of hearing patients. The level of impairment is not related to the presence of conduct disorders in hearing impaired children and youth.

Table 4. Total score of conduct disorders distributed by time of origin of hearing loss

Time of occurrence of the hearing impairment	N	AS	SD	T	df	p
Prelingual	141	20.67	5.10	0.449	167	0.654
Postlingual	28	20.18	5.59			

The analysis of the total scores of conduct disorder shows that in a sample of individuals with hearing loss there was no statistically significant difference ($p = 0.654$) between patients who had hearing loss caused prelingually and postlingually. Time of occurrence of the hearing impairment was not related to the presence of conduct disorders in hearing impaired children and youth.

Analysis of the total scores of conduct disorder in relation to gender shows that there is a statistically significant difference ($p = 0.003$) in the expression of conduct disorders among boys and girls with hearing impairment. Male respondents expressed a greater presence of behavioral disorders.

Table 5. Total score of conduct disorders in boys and girls with hearing impairment

Gender	N	AS	SD	t	df	p
Male	102	21.55	5.127	3.072	149	0.003
Female	67	19.12	4.86			

Table 6. T test for items in which we found statistically significant difference in the manifestations of conduct disorders in boys and girls with hearing impairment

Item	Gender	AS	SD	T	df	p
Prone to physical cruelty toward younger and weaker students	Boys	1.73	0.80	3.408	166	0.001
	Girls	1.37	0.55			
Prone to purposefully annoy others	Boys	1.75	0.78	3.954	164	0.000
	Girls	1.33	0.59			
Tends to threaten, intimidate and harass other	Boys	1.29	0.48	2.811	147	0.006
	Girls	1.09	0.45			
Prone to fights	Boys	1.50	0.66	4.359	165	0.000
	Girls	1.12	0.48			
Destructive towards common things (eg. School inventory)	Boys	1.26	0.45	3.457	160	0.001
	Girls	1.06	0.24			

Table 7. Total score of conduct disorder scores assigned to the school success of children and youth with impaired hearing

Academic achievement	N	AS	SD
Weaker and average grades in school	32	23.34	5.59
Very good grades in school	45	21.87	6.24
Excellent grades in school	92	19.00	5.24

Table 8. Analysis of variance for scores on a scale of conduct disorders in general assigned to the school success

	The sum of squares	df	Average square	F	p
Between groups	548.587	2	274.294	11.219	0.000
Within groups	4058.419	166	24.448		
Total	4607.006	168			

Analysis of variance showed a statistically significant difference between the cumulative score on a scale of conduct disorders among respondents with hearing impairments in relation to school success ($p = 0.000$). Respondents with lower school achievement are more likely to express conduct disorder than those with better school achievement.

Given the established statistical significance of difference between the better and worse hearing impaired students, the T test for items in which statistically significant difference was found.

Table 9. T test for items found in which a statistically significant difference in the manifestations of conduct disorders among groups with different academic success was found

Item	The sum of squares		df	The average of squares	F	p
Prone to physical cruelty toward younger and weaker students	Between groups	6.738	2	3.369	6.798	0.001
	Within groups	82.268	166	0.496		
	Total	89.006	168			
Prone to purposefully annoy others	Between groups	4.294	2	2.147	4.102	0.018
	Within groups	86.877	166	0.523		
	Total	91.172	168			
Tends to threaten, intimidate and harass other	Between groups	1.187	2	0.933	4.249	0.016
	Within groups	36.465	166	0.220		
	Total	38.331	168			
Prone to fight	Between groups	2.744	2	1.372	3.694	0.027
	Within groups	61.658	166	0.371		
	Total	64.402	168			
Destructive towards common things (eg. School inventory)	Between groups	1,314	2	0.657	4.414	0.014
	Within groups	24.710	166	0.149		
	Total	26.024	168			
Destructive towards other persons's things	Between groups	2.202	2	0.101	3.991	0.020
	Within groups	45.798	166	0.276		
	Total	48.000	168			
Prone to theft	Between groups	1.923	2	0.961	5.865	0.003
	Within groups	27.213	166	0.164		
	Total	29.136	168			
Prone to lying from personal reasons	Between groups	7.657	2	3.829	10.489	0.000
	Within groups	60.591	166	0.365		
	Total	68.249	168			
Unexcused absence from school	Between groups	6.974	2	3.487	9.628	0.000
	Within groups	60.126	166	0.362		
	Total	67.101	168			
Tantrums	Between groups	4.797	2	2.389	7.212	0.001
	Within groups	55.203	166	0.333		
	Total	60.000	168			
Often opposition and strife in relationships with adults	Between groups	3.109	2	1.554	4.308	0.015
	Within groups	59.897	166	0.361		
	Total	63.003	168			

Analysis of the total scores of conduct disorder in the scale shows no statistically significant difference ($p = 0.341$) between patients who live with their families and those

living in a boarding school for children and youth impaired in relation to the presence of conduct disorders.

Table 10. Total scores of conduct disorder assigned to the residence of children and youth with hearing impairments

Residence	N	AS	SD	t	df	P
Family	107	20.88	5.67	0.954	167	0.341
Boarding school	62	20.08	4.40			

Table 11. Total scores of conduct disorder assigned to age of the respondents

Age	N	AS	SD
7-10	45	19.82	4.30
11-14	67	20.97	5.43
15-18	57	20.74	5.69

Table 12. Analysis of variance for the total score of conduct disorder scores assigned by age of the subjects with hearing impairment

	The sum of squares	df	The average of squares	F
Between groups	37.435	2	18.718	0.680
Within groups	4569.571	166	27.528	
Total	4607.006	168		

Table 13. Total score of conduct disorders distributed by educational level of the father of respondents

Educational level of father	N	AS	SD
Primary School	50	21.40	5.62
Trade school	47	21.43	5.77
High school	62	19.82	4.59
Higher or university degree	10	17.30	1.77

The results show that there is no statistically significant difference ($p = 0.508$) in the total score of conduct disorders among subjects with impaired hearing of different age.

The table shows that there is no normal distribution of the variable of educational level of the father of the hearing impaired subjects. Fathers of children and youth with hearing impairments with college or university education comprise just over 6% of this part of the sample.

Table 14. Analysis of variance for scores on a scale of conduct disorders in general distributed by educational level of father of respondents

	The sum of squares	df	The average of squares	F	p
Between groups	210.368	2	70.123	2.632	0.050
Within groups	4396.638	166	26.646		
Total	4607.006	168			

Analysis of variance showed that the differences in the educational attainment of fathers of those with hearing loss is at the limit of statistical significance ($p = 0.050$). Children and young people with hearing impairment from lower educational and socio-economic conditions are somewhat more likely to express conduct disorder.

Table 15. T test for the item in which was a statistically significant difference was found in the manifestations of conduct disorders in patients whose fathers have different educational level

Item	The sum of squares		df	The average of squares	F	p
Prone to lie for personal gain	Between groups	3.507	3	1.169	2.979	0.033
	Within groups	64.741	165	0.392		
	Total	68.249	168			

Discussion

Results of this study show that children and adolescents with impaired hearing are not more prone to conduct disorder than children and youth with no impairments as indicated by the total score on a scale that measured the presence of conduct disorder (Table 1). However, analysis of the individual items of the instrument shows that children and youth with hearing impairments showed statistically more emphasized some manifestations of conduct disorders (Table 2). It is the tendency of theft and extortion of money or benefits from younger or weaker students.

The findings of our study are not in accordance with the highest number of surveys that provide information that in children and youth with hearing impairments the problematic behavior is more present, no matter how they are defined, such as: behavioral problems, antisocial behavior, externalized problems, etc. Conduct disorder, as defined by ICD-10 refers, for its quality and intensity of the serious developmental problems and in this fact should be sought the explanation of our findings. Namely, the used definitions indicate more severe developmental problems than those tested in alleged researches (Schlesinger & Meadow, 1971 Freeman, et al., 1975; Meadow, 1980; van Eldik et al., 2004; Vostanis, et al., 1997). Studying developmental problems and psychopathology in children and adolescents with hearing impairments, the authors did not specifically directed their attention to the conduct disorder, as was the case with this research. Authors Prinstein & La Greca (2004) argue that the results of the study depend on how the phenomenon that is being studied is defined (ie, delinquency, aggression, illegal offenses, and nonspecific outcomes).

On the other hand, the results on variables that are assumed to be related to conduct disorders in hearing impaired in children and young people are in accordance with the findings and theoretical assumptions about the development of conduct disorder.

Our findings indicate that conduct disorder in children and adolescents with hearing impairments, in relation to the gender of the respondents - male respondents expressed a greater tendency to disorder behaviors than female respondents. Published studies (Peterson, 1961; Friedrich et al., 1984, Kerr et al. 2004; Björkqvist et al., 1992, Cohen et al. 1993; Crick, 1995; Grotperter & Crick, 1995; Feehan et al. 1994; Offord et al., 1987, Lahey et al., 2000,

Loeber & Keenan, 1994;) on gender differences in the presence of behavioral disorders, are consistent with our results.

In addition, the findings of our studies are consistent with the findings (Bardone et al. 1996; Stott, 1981; Hawkins et al., 2003, Masten, et al., 1995, Williams & McGee, 1994; Dodge & Pettit, 2003; Hinshaw, 1992; Maguin & Loeber, 1996; Hinshaw & Anderson, 1996) that show that children and youth of lower academic achievement are more likely to express behavioral disorder.

The results of our research show that children and young people with hearing impairment who come from lower socio-economic status, if it is used as an indicator of educational level of their fathers are more prone to disorder behaviors than those from higher status families. Our findings are consistent with studies (Lahey et al., 1999, Sampson et al., 1997) on expressed emergence of behavioral disorders in families of lower socio-economic position.

The assumptions that the variables (degree of hearing loss, the time of occurrence of hearing loss and accommodation during training - a boarding school or family) are related to conduct disorders in hearing impaired children and youth are not confirmed. Also, the age of subjects is not related to the presence of behavioral disorders in children and adolescents with hearing impairment.

The value of the findings of this study is that they suggest that in the development of conduct disorders in children and adolescents with hearing impairment the specific patterns that are related specifically to the loss of auditory communication channels are not needed. The presence of the conduct disorder is more pronounced in boys, children and adolescents of lower school achievement and those from families of lower socioeconomic status. It seems that the presence of conduct disorders in childhood and adolescence is not characteristic for children and youth with hearing impairment, that is in conjunction with the hearing loss.

On the other hand, it should be considered that the diagnosis the disorder involves severe forms of antisocial behavior. Impacts of variables related specifically to children and youth with hearing impairments may be identified with less serious forms of maladaptive behaviors (eg. externalized behavioral problems).

Limitations

This study had a number of limitations. The study did not take into account the many variables that are associated with conduct disorders in children and adolescents. One of the most important, as we consider, is relation with parents and the general situation in family. This is related to a second limitation of the research. It has failed to learn the impact of specific characteristics of families of children with hearing impairments (primarily a way of communication and acceptance of a deaf child) that can be assumed to have effects on the development of conduct disorder. Research has failed to examine the relationship or other potentially relevant variables related to hearing loss (the time of initiation of rehabilitation, the development of sign language, the linguistic peculiarities and speech development). The study sample consisted of children who are educated in special forms of education, including isolation, lack of contact with normal hearing population, reduced educational expectations, and low assessment criteria and so on) or circumstances that may have affected the results of the research. Also, we were not able to attach the control related to the general characteristics of the environment (poor economic situation, transition, disrupted the system of values, the

characteristics of the educational system) that could affect children and young people with hearing impairments and those without damage. Given that the environment variables are considered as possible determinants of the disturbance of conduct, we believe that their consideration in this research would be desirable.

Praxis Implications

The results of this study have implications relating to work with children and youth with hearing disorders and the prevention of potential developmental disorders and later psychopathology. Although the survey results did not indicate the prominent conduct disorder in children and adolescents with hearing impairment, we should not ignore the fact that certain indicators are more present than in children and young people without hearing loss. It would be important to check to what extent the presence of these indicators is a consequence of boarding lifestyle and isolated education that is available to a large number of children and youth with hearing impairments in Serbia.

Prevention programs that are expected to be able to have a positive impact on reducing the risk factors for occurrence of conduct disorders in children and adolescents with hearing impairments are related to psychosocial interventions. In schools for children and youth with hearing impairment it is advisable to conduct additional sports activities (especially for boys), and consider the possible positive impact of martial arts that would help control aggression and destructiveness. Art therapy and projective, non-directive non-verbal therapeutic techniques may be considered desirable for all children and youth with hearing impairments. In those who have stronger risk factors for occurrence of conduct disorders the additional psychotherapeutic intervention and family support is required. Prevention programs should be directed to the environment of children and youth with hearing impairments, particularly for reducing prejudice, given the research results (Dimoski, et al., 2013) demonstrated the presence of indifference and resistance to children and youth with impaired hearing. Preventive interventions for improving the academic achievement of children and young people with hearing impairment, according to research findings (e.g., Hawkins, Catalano, Kosterman, Abbott, & Hill, 1999) are in relation to a reduced risk of developing behavioral problems, including conduct disorders. Positive interventions in the education system in Serbia may have a potential very large positive impact because it would contribute to the development of inclusive trends that are still in their beginning. These changes would have a positive effect on strengthening the implicit self-esteem of children and youth with hearing impairments, reducing the risk of developing psychopathology, developmental age, including behavioral disorders.

CONCLUSION

This study did not find that children and young people with hearing impairments in Serbia have a higher presence of conduct disorders compared to children and youth with no damage. Findings suggest similar patterns of development of conduct disorders, regardless of hearing damage, since that established correlates of conduct disorders in hearing impaired

children and young people this research detected with hearing population. Since conduct disorder involves serious manifestations of antisocial behavior, future research should examine the presence of developmental disorders that are characterized by less severe symptoms (externalizing disorder, behavior problems, socio-emotional problems) in children and adolescents with hearing impairment and determine any specificity in the occurrence related to hearing loss (method of communication during start-up and success of rehabilitation, acceptance of violence, experience with normal hearing peers, etc.). Also, future research should examine the presence and effects of risk factors of disturbance behaviors that have already been established in children and adolescents without impairments and their impact on children and young people with hearing impairment.

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Chapter 28

SUDDEN SENSORINEURAL HEARING LOSS AND POLYMORPHISMS IN IRON HOMEOSTASIS GENES

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ABSTRACT

Sudden sensorineural hearing loss (SSNHL) is an important cause of acquired hearing deficits in the adults. Several pathophysiological hypothesis have been proposed so far, however the cause of sudden hearing loss is still unclear. Even if local hypoxic/ischemic events as well as inner ear viral infection have been reported to be the main hypothesis leading to transient or permanent cochlear dysfunction, and therefore to Sudden Sensorineural Hearing Loss, still there are other hypothesis that have been claimed.

Aim of the present study is to investigate about the possible role of iron metabolism, and in particular about the presence of genetic variants of the principal iron-related genes, and acute inner ear disorders such as sudden sensorineural hearing loss.

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) represents an acute inner ear disorder, mostly unilateral, that generally affect adults worldwide, even if higher occurrence rates are reported in developed countries [1, 2]. It has been estimated that SSNHL has an overall incidence rate of 5–20 / 100,000 individuals per year, though this is most likely an underestimate [2, 3].

Several pathophysiological mechanisms for idiopathic SSNHL have been proposed in the literature. The most reported are: local hypoxic/ischemic events (such as coagulopathies,

vascular hypotension and thrombo-embolism), autoimmune disorders, metabolic diseases, viral inner ear infections, rupture of the inner ear membranes, free radicals induced-damage, neuronal damage and dysregulation of the local inflammatory response [3-5] leading to transient or permanent dysfunction of cochlear microcirculation [6].

Since iron has been linked to oxidative stress, we hypothesized that iron metabolism regulatory genes could have a role in the homeostasis of the oxidative balance also in the inner ear and, consequently, in the pathophysiology of acute inner ear disorders such as SSNHL.

Aim of this chapter is to focus on the possible role of divalent metallic ions, and in particular on the presence of genetic variants of the principal iron-related genes, in the aetiopathogenesis of SSNHL [7].

METHODS

The Pubmed database was searched up to September 2014 (going back for 10 years); full text articles were obtained when the title, abstract or key words suggested that the study may be eligible for this study. The search was carried out independently, and restricted to papers in English language. Other papers were also identified from the references in the published literature.

The medical subject heading (MeSH) used included: Sudden Sensorineural Hearing Loss, Iron metabolism, Iron Homeostasis, Iron genes, Oxidative stress, Inner ear.

IRON METABOLISM AND OXIDATIVE STRESS

There is a growing interest in the possible association between iron metabolism and oxidative stress, as it has been reported that local iron excess is a potential cause of increased oxidative stress and therefore could be involved in cellular injury and death. Iron is an essential nutrient, but its divalent form (Fe^{2+}), as well as other divalent metal ions, also retains the capacity to enhance redox cycling and free radical formation [8, 9]. Iron-mediated oxidative stress is hypothesized to be involved in the pathogenesis of several degenerative disorders, including thrombosis, venous ulcers, chronic venous disease, and central nervous system disorders such as multiple sclerosis and other neurodegenerative diseases, or neoplasms [10-13]. In addition, a novel iron-driven aetiopathogenetic mechanism, responsible for increase free radical generation, has been formulated in degenerative skin lesions appearance comprehending coexistence of local iron overload and iron homeostasis gene variants [14]. Similar conditions could also be potentially associated with sudden hearing loss [15]. So, divalent ions homeostasis could be a central pathway involved in the pathophysiology of sudden hearing loss [16, 17, 18].

The main genes and their variants that could be possibly involved in the aetiopathogenesis of SSNHL are described below [10, 19].

The *HFE gene* (6p21.3-22.2) encodes a membrane protein of 348 amino acids that belongs to the MHC class I family. The protein is normally expressed in cryptal enterocytes of the duodenum, liver, placenta, kidney, central nervous system, plasma and platelets. By

complexing with beta 2 microglobulin and transferrin receptor 2 (TFR2), it plays a crucial role in iron homeostasis, and, when mutated, it is believed to be responsible for hemochromatosis, variegate porphyria and microvascular complications of diabetes. Gene variants and/or mutated proteins bind to the transferrin receptor and reduce its affinity for iron-loaded transferrin. Thus, they finally unbalance the iron intake. Recent increasing interest in neuro-degenerative disorders mediated by iron overload, have highlighted the HFE gene among candidates for further investigations into iron homeostasis involvement in similar conditions. A review of the literature suggests a potential role even in iron-mediated hearing loss also in the past [20, 21]. Finally, it is important to note that the HFE gene is also expressed in the brain, spinal cord, cortex and cerebellum [22, 23]. Thus, it could be directly involved or responsible for specific conditions concerning the central nervous system.

The *FPN1 (SLC40A1)* gene is located on chromosome 2 (2q32.2), and it encodes a protein (ferro-portin) of 570 amino acids with the specific function of exporting iron out from cells in the basolateral space, except for the reticulo-endothelial cells, which can spread iron ions into the blood circulation. Consequently, FPN1 plays a crucial role in iron homeostasis [24], and, generally, it has the opposite function of the divalent metal transporter 1 (DMT1) protein product [25], which allows intracellular passage of divalent iron (Fe^{2+}). Ferroportin is expressed in different tissues, brain and spinal cord included, though to the best of our knowledge, there are no previous reported studies that document its localization specifically into the cochlea. Similar to other iron genes, it undergoes iron regulation at the transcriptional and translational level [26-28].

Another important gene related to ferroportin expression and function is the *HEPC gene (19q13.1)* encoding the protein Hepcidin Anti-Microbial Peptide (HAMP). This protein is a 25-amino acid peptide, derived from the cleavage of an 84-amino-acid long pro-peptide that is mainly synthesized by hepatocytes, but it is expressed also in brain, spinal cord, cortex and cerebellum included. HEPC is the major regulator of iron balance activity via binding to the FPN1 protein on the cell membrane, sup-pressing it [29, 30]. HEPC expression and its role in iron homeostasis may play a crucial role in dif-ferent conditions [31].

The *TF gene (3q22.1)* encodes for the protein transferrin, which forms a stable complex with the HFE protein, which facilitates iron transfer via the transferrin receptor. The function of this protein is to transport iron from the intestine, reticuloendothelial system, and liver parenchymal cells to all proliferating cells in the body. Tansferrin is expressed in different tissues, brain, spinal cord included, cortex and cerebellum included. The effect of HFE on iron absorption depends on its relationship with the transferrin receptor. HFE variants affect TF binding, determining a loss of HFE-repressor function for TF uptake, thereby increasing iron transport within the cells [32-34].

IRON METABOLISM AND THE INNER EAR

Sudden hearing loss has been reported to be associated with a huge number of clinical conditions and its aetiopathogenesis is still unclear [35-38]. The uncertainty of reasonable etiologies has encouraged continuous investigations aimed at identifying the most convincing pathological explanations. Far from the identification of an unequivocal mutated gene, the study of genetic variants of several conditions has attracted several researchers even if a

specific correlation between a precise inner ear gene mutation and SSNHL still has to be proved. Some studies have reported a correlation of various polymorphisms with an increased [39-43] or reduced [44] risk of developing hearing impairment.

Recent findings concerning ROS-mediated damage, NO activity and inner ear iron metabolism have encouraged researchers to focus their studies on possible connections between microvascular damage and free radical production in the inner ear [45-47, 49]. In this sense, some have speculated that polymorphisms of genes related to iron metabolism, such as FPN1 (SLC40A1) gene, the HFE gene or the TF gene, could be involved in the pathogenesis of some acute inner ear disorders, such as sudden sensorineural hearing loss [47,48,49]. Of particular interesting are the observations among iron metabolism within the stria vascularis. Stria vascularis is particularly sensitive to free radical stress due to its high metabolic activity and dense vascular system [50], and, consequently, when iron chelator proteins are not adequately functioning to contrast and neutralize the damaging effect of iron and linked free radicals, its function can be dramatically impaired, therefore hampering inner ear homeostasis [50]. The significant presence of ferritin [47] and DMT1 [48,49], within the cochlear stria, suggest that these proteins have an active role in restoration and deposition of iron, and can retain a role in reducing the endolymphatic concentration of divalent ions [51, 52]. In fact, preliminary experimental studies on mouse models have shown that free radical stress, induced by the loss of specific protein expression related to iron metabolism in stria vascularis, cause hearing loss [18]. It is possible to speculate that polymorphism of genes related to iron metabolism such as FPN1 (SLC40A1) gene, or of the HFE gene or the TF gene, could possibly contribute in altering the inner ear oxidative homeostasis.

Apart from the stria vascularis, the exact location of the proteins involved in the metabolism of iron, within other inner ear settings, is still not clear. The identification of their position could offer indications in understanding how iron metabolism works within the inner ear oxidative homeostasis.

Unfortunately, the knowledge among the iron metabolism within the inner ear is still very limited; further experimental studies are necessary in order to understand which could be its role within the inner ear homeostasis.

IRON METABOLISM AND SUDDEN SENSORINEURAL HEARING LOSS

So far, there are no clinical evidences to support this association, clinically. Only very few studies have claimed a relationship between these two conditions. In particular, Chung et al. have observed a relation between SSNHL and iron deficiency anemia [53]. Also, Sun et al. described significant improvements in clinical results using iron therapy in patients with SSNHL [54]. However, their clinical success only warranted the use of iron therapy in managing SSNHL, and their limited case numbers meant that the relationship between patients affected by iron deficiency anemia and SSNHL should still be further elucidated [54].

Even if the few available studies on animal models seem to encourage this hypothesis as described in the previous paragraph, the aetiopathogenetic mechanism that links the onset of an acute inner ear disorder, such as SSNHL, and iron metabolism is still far to be understood, though it can be an intriguing hypothesis.

CONCLUSION

In conclusion, clinical and genetic studies are required to further elucidate the pathophysiological mechanisms of SSNHL. Such a complex disease is to consider a multifactorial and polygenic condition in which gene-environment interactions have a key role. In particular, considering the possible link between iron metabolism and inner ear oxidative stress, more efforts should be performed in order to better understand the complex biochemical environment and mechanisms of the inner ear.

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Chapter 29

CHRONIC TINNITUS: PITCH, LOUDNESS, AND DISCOMFORT IN ADULTS AND ELDERLY PATIENTS

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ABSTRACT

Tinnitus is a common symptom in individuals of various age groups, but the impact it causes is variable, depending on the characteristics of subjects. The aim of this study is to analyze the characteristics of tinnitus and the discomfort it causes in individuals assessed in a specific outpatient clinic in a tertiary hospital. Participants were evaluated by medical history interview, medical examination, grading of tinnitus severity, hearing screening and testing, measurement of tinnitus pitch and loudness and THI instrument for identifying tinnitus discomfort. The sample consisted of 199 individuals; 124 of them (62.30%) were females, with a mean age of 58.18 ± 12.79 years, with bilateral tinnitus (50.8%) and average length of tinnitus presence was 5.18 ± 4.67 years. Tinnitus pitch was acute and tinnitus loudness was moderate, within the values reported in the technical literature. Mean tinnitus severity was 5.18 ± 4.67 years and the THI score ranged from 0 to 98 points (mean 40.03 ± 25.48 points). No difference was observed between THI scores and sex and tinnitus location. Correlation was observed between tinnitus severity

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and THI scores, between age and tinnitus loudness in the left ear, and between age and THI scores.

INTRODUCTION

Tinnitus is a common symptom in medical and audiological exams. It is defined as the sound perceived by the subject without an external source being present. [1,2] It may be caused by otological, neurological, cardiovascular, rheumatological, endocrine, metabolic and immune diseases. Trauma, temporomandibular joint disorders, psychological problems and use of ototoxic medication are also causes of tinnitus. [2,3]

Tinnitus can be graded in several ways. Tinnitus can be considered as subjective (perceived only by the affected individual) or objective (perceived by others), continuous or intermittent, pulsatile or non-pulsatile, unilateral or bilateral or located in the center of the head. The onset may be sudden or insidious. [2,4] Grading is used by health professionals to categorize the symptom as shown by individuals. It assists in determining etiology and treatment.

The prevalence of tinnitus varies depending on the population studied. A study conducted in South Korea showed that 19.7% of individuals aged 12 years or older had the symptom. [5] Another study with Japanese elderly showed that 18.7% of them had tinnitus. [6] In Egypt, the prevalence was 5.17% and in the United States, 25.3%. [7, 8] The prevalence of tinnitus in the elderly is higher than in adults, with values ranging between 33% and 72.5%. [9,10] General data show that in 2004, tinnitus affected 15% of the world population, [11] and its prevalence increased to 25.3% in 2012. [12]

Although it is a more frequent complaint by adults and the elderly, children can also have tinnitus. Research conducted in Brazil showed a high prevalence of tinnitus in children. In a study that evaluated 477 children, continuous tinnitus was found in 21.7% and pulsatile tinnitus in 3.8% of them. [13] Another more recent study showed that 54.7% of the children interviewed had had tinnitus for the past 12 months. [12]

The relationship between tinnitus and gender of affected individuals is still controversial in the literature. [14] Some studies showed a similar number of affected individuals, [6, 14] while others showed a higher prevalence of women [10, 15, 16] or men. [17, 18, 19]

Despite the high prevalence of tinnitus, the discomfort it causes is variable, because some individuals reported tinnitus but their activities were not affected by the symptom, while others reported severe problems. [2, 19] It is believed that approximately 20% of tinnitus patients feel discomfort. [20] Factors such as personality traits, depression, anxiety, difficulty in dealing with problems, and concentration difficulties influence the level of discomfort caused by tinnitus. [21, 22] It is actually a prognostic factor for treatment.²³ Thus, primary psychological factors influence the level of discomfort and the result in the treatment of tinnitus. [4, 14, 20] Patients' concern about tinnitus is crucial for adapting to it, and there may be a vicious circle that patients cannot cope with. [14]

On the same line of reasoning, depression can be caused by tinnitus, but it can also be indicative of poor adaptation to it. [24] Likewise, sleep disorders may be caused by tinnitus, but they could also exist prior to the appearance of the symptom, i.e., they could be a comorbidity rather than a consequence of it. [14] These and other disorders (anxiety and stress, for example) lead to loss of quality of life, which is widely described in the literature. [2, 23, 25, 26] However, in a study with subjects outside the hospital or clinical environment, there was no influence of tinnitus on quality of life. [17] This seems to reinforce the idea that

the discomfort and the consequences of tinnitus are related to the psychological aspects of individuals.

Research conducted to date showed no influence of the variables age and gender on discomfort caused by tinnitus. [14, 20]

The evaluation of individuals with tinnitus aims to define the etiology and treatment of it. It is supposed to include detailed history, physical examination, laboratory tests, audiological evaluation and radiological assessment. [27] Moreover, questionnaires should be used to determine the impact of tinnitus on a patient's life. The Tinnitus Handicap Inventory (THI) is one of the most used, and it has already been translated, adapted and validated into several languages. Originally created in the English language, [28] it has versions in Brazilian Portuguese [29], Chinese - Mandarin and Cantonese [30, 31], French, [32] Italian, [33] Spanish, [34] Filipino [35] and Persian, [36] among others.

THI is composed of 25 questions for assessing the effects of tinnitus in the restriction of daily activities of affected individuals. [37] There are three types of response for each situation: Yes (4 points), Sometimes (2 points) or No (0 points). The sum of points obtained in each response allows one to assess the level of discomfort caused by the symptom: slight (0-16 points), mild (18-36 points), moderate (38-56 points), severe (58 to 76 points) and catastrophic (78-100 points). [14] Because it is quick and easy to apply and interpret, addresses the influence of tinnitus on a patient's life, and has adequate validity and reliability, THI is routinely used in the clinical evaluation of patients. [28, 38]

Although tinnitus is studied by researchers from various countries, further research about tinnitus and its effects is still needed, especially in light of the contradictions in the literature. Thus, the objective of this study is to analyze the characteristics of tinnitus and the discomfort it causes in subjects evaluated in a specific outpatient clinic in a tertiary hospital.

METHODOLOGY

This was a cross-sectional study conducted in a tertiary care hospital in southern Brazil. The sample consisted of both male and female patients suffering from chronic tinnitus and history of tinnitus discomfort, who were seen in a specific outpatient clinic. The presence of the symptom for a period of time greater than six months was defined as chronic tinnitus. [26]

Patients were evaluated by otolaryngologists and audiologists who determine the presence of hearing loss, tinnitus characteristics, the etiology of it and the presence of other comorbidities, such as depression, anxiety, metabolic disorders, etc.

ENT evaluation consisted of medical history interview, physical examination and otoscopy. After that, patients were evaluated by audiologists through pure tone audiometry testing of hearing thresholds for high frequencies and conventional frequencies, speech audiometry, acuphenometry, measurement of loudness discomfort levels and acoustic immittance. Next, patients underwent laboratory tests and imaging tests, if necessary.

The medical history interview, conducted through oral questions to be answered by patients, investigated sociodemographic data (age, gender, race), health history (diseases, medication use) and tinnitus history (length of symptom presence, laterality, improvement or worsening factors, etc.). Patients were also asked about tinnitus severity. Patients were asked:

“On a 0-10 scale, how much does tinnitus bother you in your life?”. After that, the version of the THI instrument that was validated and translated into Portuguese. [29]

Then, patients underwent audiological evaluation, and a complete audiological evaluation was made. At first, all patients underwent pure tone audiometry; conventional frequencies and high frequencies were measured. The examination was conducted in a soundproof booth, and thresholds were measured by air (250Hz to 16000Hz) and bone conduction (500Hz to 4000Hz). Then, acuphenometry was performed. It is a subjective measurement of tinnitus pitch and loudness, since it is not possible to objectively measure the intensity and frequency of the symptom.

Pitch corresponds to the sense of frequency and loudness to the sense of intensity of tinnitus reported by the patient. Patients were asked to compare their tinnitus to sounds emitted by the audiometer (pure tone or narrow band noise). [39] Acuphenometry was performed according to the procedure described by Branco-Barreiro. [40] Initially, pitch was measured. The hearing threshold of patients was selected in all frequencies, 10dBNA were added, and either pure tone or noise was presented, depending on patients' description of the characteristics of their tinnitus. Patients were asked to raise their hand when they realized that the sound they heard was similar to their tinnitus. After that, loudness was measured. The stimulus (pure tone or noise) was presented at the frequency indicated by the patient as similar to tinnitus, with initial intensity of 10dBNA below the patient's threshold. Then, intensity was increased 2dBNA at a time, and patients were asked to raise their hand at the time realized that the intensity presented was similar to that of their tinnitus. Such intensity was recorded and subtracted from the individual's hearing threshold. This calculation determined tinnitus loudness.

After that, the following measurements were performed: loudness discomfort levels, acoustic immittance, with tympanometry and contralateral and ipsilateral acoustic reflexes, transient evoked otoacoustic emissions and distortion product otoacoustic emissions. In specific situations, patients were evaluated for auditory evoked potentials.

After the completion of all tests, the subjects underwent medical evaluation again to determine the etiology and appropriate treatment for each case.

This study focuses on results of the evaluation of patients through acuphenometry, considering tinnitus pitch and loudness. Patients who had all assessments described above were included in the study.

The analysis was done by descriptive quantitative statistics, considering the absolute and relative values of the variables studied. The comparison of the results for THI between the groups used non-parametric tests (Mann-U-Whitney and Kruskal-Wallis), because the variable follows a non-normal distribution. To study the correlations between variables, the Spearman correlation coefficient was used.

RESULTS

Examinations were evaluated for 199 patients seen at the chronic tinnitus outpatient clinic. According to data shown in Table 1, the highest prevalence was in females (62.3%), the mean age was 58.18 ± 12.79 years, with bilateral tinnitus (50.8%). The length of presence of the symptom ranged from less than one year to 32 years, with a mean time of 5.18 ± 4.67

years. Mean tinnitus pitch in both ears was approximately 4000Hz, while mean loudness was approximately 15dBNA. THI scores showed a mean of 40.03 ± 25.48 . However, the analysis of grading by the instrument showed a greater number of individuals with slight, mild and moderate discomfort levels. In comparison, the grading of tinnitus severity, by the question about this, showed that subjects graded the discomfort caused by tinnitus between 2 and 10 points, averaging 5.18 ± 4.67 points.

Table 1. Descriptive analysis of the sample

Variables	N	%
Gender		
Male	75	62.3
Female	124	37.7
Age (years)		
Average $\pm$ standard deviation	58.18 ± 12.79	
Minimum - Maximum	19 - 82	
Time of tinnitus (years)		
Average $\pm$ standard deviation	5.18 ± 4.67	
Minimum - Maximum	0 - 32	
Location of tinnitus		
Right ear	47	23.6
Left ear	51	25.6
Both ears	101	50.8
Pitch of tinnitus (Hz)		
Right ear		
Average $\pm$ standard deviation	4359.80 ± 2735.54	
Minimum - Maximum	250 - 8000	
Left ear		
Average $\pm$ standard deviation	4458.88 ± 2678.63	
Minimum - Maximum	250 - 9000	
Loudness of tinnitus (dB)		
Right ear		
Average $\pm$ standard deviation	16.65 ± 14.99	
Minimum - Maximum	0 - 75	
Left ear		
Average $\pm$ standard deviation	15.84 ± 14.05	
Minimum - Maximum	0 - 70	
Score THI		
Average $\pm$ standard deviation	40.03 ± 25.48	
Minimum - Maximum	0 - 98	
Classification THI		
Slight	44	22.1
Mild	62	31.2
Moderate	41	20.6
Severe	31	15.6
Catastrophic	21	10.6
Gravity of tinnitus		
Average $\pm$ standard deviation	5.18 ± 4.67	
Minimum - Maximum	2 - 10	

Correlation was analyzed between the variables THI score, age, tinnitus length, tinnitus severity, tinnitus pitch and tinnitus loudness (Table 2 and Table 3). There was a positive correlation between tinnitus severity and THI score ($r = 0.32$, $p < 0.001$) and negative and statistically significant correlations between age and THI score ($r = -0.254$, $p < 0.001$), and between age and tinnitus loudness in the left ear ($r = -0.18$, $p = 0.02$). There were no correlations between other variables: age and length of tinnitus ($r = 0.08$, $p = 0.24$), age and tinnitus severity ($r = 0.11$, $p = 0.11$), age and tinnitus pitch and tinnitus loudness in the right ear ($r = -0.03$, $p = 0.67$ and $r = -0.18$, $p = 0.29$, respectively), age and tinnitus pitch in the left ear ($r = 0, 02$, $p = 0.80$), length of tinnitus and THI score ($r = 0.01$, $p = 0.78$), length of tinnitus presence and tinnitus severity ($r = -0.06$; $p = 0.38$), length of tinnitus presence and tinnitus pitch and loudness in the right ear ($r = -0.06$, $p = 0.43$ and $r = -0.24$, $p = 0.78$, respectively) and in the left ear ($r = -, 014$, $p = 0.06$ and $r = -0.33$, $p = 0.68$, respectively). Tinnitus severity was not associated with length of tinnitus presence ($r = -0.06$, $p = 0.38$), nor with tinnitus pitch and loudness in the right ear ($r = 0.00$, $p = 0, 91$ $r = -0.32$, $p = 0.70$, respectively) and in the left ear ($r = -0.49$, $p = 0.55$ and $r = 0.03$, $p = 0.63$, respectively).

Table 2. Analysis of the correlation between gender and scores on THI

	THI score			
	Average	Median	Minimum	Maximum
Female	40.3	36	0	98
Male	39.6	36	0	90

p-value – 0,82 (Mann-Whitney)

Table 3. Location of the THI score and tinnitus

	THI Score			
	Average	Median	Minimum	Maximum
Right ear	40.4	36	6	96
Left Ear	37.8	32	0	98
Both ears	41.0	36	0	90

p-value – 0,69 (Kruskal-Wallis)

Discussion

The results obtained in the study show that the sample was composed mostly by females. This finding is in disagreement with some studies that showed a similar number of men and women, [14] or a greater number of men,¹⁷⁻¹⁹ but it is equivalent to others. [10, 15, 16] In the study group, women may be considered to be more affected by tinnitus, but the data may also reflect a situation that Brazilian women seek health services more often. [41, 42]

The age of the studied subjects ranged between 19 and 82 years, with a mean of 58.18 ± 12.79 years. It was found that 121 (60.80%) patients were younger than 65 years old, which is indicative that the sample consisted primarily of adults, similar to samples of other recent studies. [18,26] The lower presence of elderly in the sample was not expected by the

researchers, since the literature reports an increase in the symptom with aging, [9] but it can be indicative of two possibilities. One is the decrease of the current age of individuals affected by tinnitus who seek specialized care. Another possibility to explain the age of treated patients is the association between tinnitus and resilience. Patients who complain about tinnitus and discomfort are seen in the outpatient clinic. It is known that elderly people have higher levels of resilience than adults, and that greater resilience is associated with less discomfort caused by tinnitus. A study on resilience showed that it is associated with better emotional health, which, in turn, stops tinnitus from having such a negative impact on quality of life. [23]

No children and adolescents were evaluated, although the technical literature reported that tinnitus can be observed in individuals of various age groups, and there is a high prevalence of children with the symptom. [12, 13] This can be explained by the fact that parents do not always know the complaints and otologic symptoms of their children, and the latter rarely report tinnitus spontaneously. [13] Thus, it is crucial for parents and health professionals who evaluate children to investigate the presence of tinnitus, so that etiology is clarified and appropriate treatment is given, since 19.6% of children may report discomfort by the presence of the symptom. [43]

The length of tinnitus presence in the subjects of the sample was 5.18 ± 4.67 years, similar to the results of one study conducted in the USA, whose sample was comprised of some Brazilian individuals. [26] Length, however, was lower than in other studies, [44-46] and most evaluated patients had bilateral tinnitus (50.8%), which is consistent with previous studies [46-48] but it is in disagreement with others, where there was a predominance of tinnitus in the left ear. [18, 26] It is believed that the results obtained in the present research, as regards tinnitus location, can be attributed to the etiology of the symptom, predominantly caused by presbycusis, noise-induced hearing loss and metabolic changes.

The study of psychoacoustic characteristics of tinnitus showed mean pitch of about 4000 Hz in both ears and mean loudness of 16.65 dB HL in the right ear and 15.84 dB HL in the left ear. The values were lower than in other studies. [45, 46] Previous studies showed an average tinnitus pitch of 6000 Hz and tinnitus loudness between 51dBNA and 61dBNA. This large difference in loudness can be explained by the evaluation method used in the studies.

THI scores ranged between 0 and 98 points, averaging 40.03 ± 25.48 points. The values were similar to those of another study. [46] The analysis of THI grading showed that most of the evaluated patients had mild discomfort (31.2%), followed by slight (22.1%) and moderate discomfort (20.6%).

The analysis of THI score and gender, and THI score and tinnitus location showed no significant differences. These data had already been described by other authors. [14, 48]

The analysis of the correlations between the characteristics of tinnitus, tinnitus discomfort and tinnitus severity showed that there was a positive correlation between tinnitus severity graded by patients and THI score. Thus, the higher the score on the scale, the greater the discomfort caused by tinnitus in the assessment made by THI. These data were expected by the researchers, since both tests evaluated the impact of tinnitus on patients' life. A similar result was obtained in a previous study which analyzed the relationship between the responses from THI and the visual analogue scale. [38]

There was also a negative and significant correlation between age and THI score, indicating that the higher the age, the lower the score. The analysis of these data and the fact that there was no correlation between age and most psychoacoustic characteristics of tinnitus

(pith and loudness), seem to confirm that individuals adapt more easily to the symptom as they grow older. Again, resilience must be taken into account. [23] These data, however, differ from results of other studies that used the same instrument to assess the impact of tinnitus and found no relationship between age and THI score [18, 20,48, 49] or even an increase of the impact of tinnitus with increasing age. [47]

CONCLUSION

Data analysis has shown that the majority of the sample was comprised of female adults who had had tinnitus for about five years in both ears. Tinnitus pitch was acute and tinnitus loudness was moderate, within the values reported by the technical literature. The discomfort caused by tinnitus was mostly mild, slight or moderate, and subjects rated the discomfort caused by tinnitus as grade 5.

No difference was found between THI scores and gender and tinnitus location. There was correlation between severity of tinnitus and THI score, between age and tinnitus loudness in the left ear, and between age and THI score.

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Chapter 30

EFFECT OF HEARING LOSS ON TRAFFIC SAFETY AND MOBILITY

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ABSTRACT

Research into the effect of hearing loss (HL) on traffic safety and mobility is limited and the empirical findings are somewhat inconsistent. HL is one of the most frequent sensory deficits in humans, leading to loss of auditory information, which may affect behavior in traffic situations and might reduce traffic safety and mobility. The prevalence of age-related HL in Europe is roughly 30% for men and 20% for women at the age of 70 years, and 55% for men and 45% for women at the age of 80 years. The prevalence of age-related HL is increasing, and as a consequence the number of road users with HL will also increase.

The aim of this PhD thesis was to investigate traffic safety and mobility for individuals with HL. Three studies were conducted: 1. a questionnaire survey aimed to evaluate differences in choice of transportation that might be related to HL, 2. a driving simulator study that looked into compensatory strategies and evaluated the efficiency of a tactile signal to alert the driver, and 3. a field study to evaluate these effects in real traffic and to evaluate a navigation system with a supportive tactile signal.

The results of the three studies indicate that there are effects of HL on traffic safety and mobility. The effects are relatively small and often bound to driving complexity; but, systematic and consistent in replicated study. Differences in transportation habits related to HL include less likelihood of having a driver's license and a higher valuing of written information, with the latter possibly prioritized before time and safety issues. Moreover, respondents with more HL were less concerned about the effects of HL, which suggests that they might be using compensatory strategies.

In the experimental studies, differences in driving behavior related to HL were bound to driving conditions and occurred when the complexity of the driving task increased. There was also an effect of HL on visual behavior, indicated in the simulator and confirmed in the field study, suggesting that drivers with HL have more active visual behaviors with more frequent glances in the rear-view mirror and a general scanning of the environment before looking away from the road. A tactile signal in the driver seat was

found useful in both experimental studies, both for calling for the driver’s attention and facilitating navigation using a GPS navigation device.

It was concluded that there are effects of HL on both traffic safety and mobility, consistently pointing toward a generally more cautious driving behavior with the use of both compensatory and coping strategies, which suggests a difference in experienced safety. Compensatory strategies associated with HL include driving at lower speeds and using a more comprehensive visual search behavior. Coping strategies associated with HL include engaging less in distracting activities. Evaluation of the tactile signal suggests that it may make driver assistance systems more accessible, not only to drivers with HL, but to all drivers. At the same time, the systems might become more effective for all users, since visual resources can be more focused on the road, which could increase both traffic safety and mobility in general.

LIST OF PAPERS

Paper I: Thorslund, B., Peters, B., Lyxell, B., & Lidestam, B. (2013). The Influence of Hearing Loss on Transport Safety and Mobility. *European Transport Research Review*, 5(3), 117-127.

Paper II: Thorslund, B., Peters, B., Lidestam, B., & Lyxell, B. (2013). Cognitive workload and driving behavior in persons with hearing loss. *Submitted to Transportation Research Part F: Traffic Psychology and Behaviour*, 21, 113-121.

Paper III: Thorslund, B., Ahlström, C., Peters, B., Eriksson, O., Lyxell, B., & Lidestam, B. (2014, May 29). Cognitive workload and visual behavior in elderly persons with hearing loss. *European Transport Research Review*, published online first, 1-9. doi:10.1007/s12544-014-0139-z

Paper IV: Thorslund, B., Peters, B., Herbert, N., Holmqvist, K., Lidestam, B., Black, A., Lyxell, B. (2013). Hearing loss and a supportive tactile signal in a navigation system: Effects on driving behavior and eye movements. *Journal of Eye Movement Research*, 6(5), 1-9.

LIST OF ABBREVIATIONS

ADAS	Advanced driver assistance system
CDT	Clock-drawing test
EF	Executive function
HL	Hearing loss
HMI	Human machine interaction
HRF	Swedish Association for Hard of Hearing People
ICF	International Classification of Functioning, Disability and Health
LTM	Long-term memory
MCZ	Multiple comfort zone model
NH	Normal hearing
OR	Odds ratio
PTA	Pure tone average
RAT	Risk allostasis theory

RHM	Risk homeostasis model
RMM	Risk monitor model
TDH	Task difficult homeostasis
TIPS	Text information processing system
TMT	Trail making test
UFOV	Useful field of view
WHO	World Health Organization
WM	Working memory

CONCEPTS AND DEFINITIONS

Age-related HL Presbycusis: The most common type of HL typically starting around middle adulthood and then progressing, particularly affecting the high frequency ranges.

Compensatory strategies: Efforts made by the individual (consciously or unconsciously) to maintain a given level of functioning despite decline in, or loss of, previously available resources

Coping strategies: Use of conscious effort to solve personal and interpersonal problems and to seek to master, minimize, or tolerate stress or conflict.

Mobility: The quality or state of being mobile. The ability to move freely.

Older adults: Individuals over 65 years

INTRODUCTION

For many people transportation is a part of everyday life and is so established that we do not think about how complex even the simplest task really is. Being a road user demands cognitive skills in order to assemble new information in the traffic environment, apply it to stored knowledge, and make decisions. This thesis examines the travel habits and driving behaviors of individuals with hearing loss (HL) and how cognitive skills interact with their driving behavior. Driving a car is a cognitively initiated and controlled task, and thus one approach to understand driving behavior is to examine how cognitive skills are involved. Cognitive psychology is the area that describes the internal processes involved in making sense of the environment and deciding what action might be appropriate (Eysenck & Keane, 2010; Neisser, 1976).

HL is one of the most frequent sensory deficits in humans, with a prevalence of approximately 10% in the general population in the western world, and it is a common chronic condition among the elderly (Stevens et al., 2013). HL entails a loss of auditory information, which may affect behavior in traffic and might reduce traffic safety. Research into the effect of HL on traffic safety and mobility is limited and the empirical findings are somewhat inconsistent. From a legal perspective, based on this relatively low level of knowledge, HL is not considered an increased traffic safety risk (Englund, 2001; Glad, 1977), and therefore hearing is not required for obtaining a driver's license for passenger cars.

From a safety perspective, some studies suggest an association between HL and increased risks of traffic accidents (Ivers, Mitchell, & Cumming, 1999; Picard et al., 2008). However,

other studies show no such relation (Green, McGwin, & Owsley, 2013; McCloskey, Koepsell, Wolf, & Buchner, 1994). Schmolz (1987) examined the importance of hearing for road users and found that HL is associated with a higher degree of inattention. With regard to attention, Hickson et al. (2012) showed that HL in older drivers was associated with poorer driving performance in the presence of distraction, but not without distraction. On the other hand, Picard et al. (2008) suggested that HL leads to a reduction in speeding violations, probably due to self-regulation. In sum, the effect of HL on traffic safety remains mostly unknown, and possibly connected to specific situations; although its associations with attention and driving speed have been shown.

From a mobility perspective, it is possible that of HL leads to self-regulation due to feelings of unsafety. This is an important aspect to consider, because mobility is important for quality of life (Farquhar, 1995), often connected to factors such as psychological well-being and independence (Bonnell, 1999; Fonda, Wallace, & Herzog, 2001; Gabriel & Bowling, 2004; Marottoli et al., 1997), and also associated with higher life satisfaction (Banister & Bowling, 2004; Hakamies-Blomqvist & Wahlström, 1998; Gagliardi, Marcellini, Papa, Giuli, & Mollenkopf, 2010).

Physiologically, disruption of any part along the auditory pathway (central to peripheral) may lead to HL and there are two main diagnoses. Problems in the outer ear (such as blockage of the ear canal) or middle ear (such as ossicular chain discontinuity) cause conductive hearing loss, and problems in the inner ear (such as loss of outer or inner hair cells in the cochlea) or problems in the auditory nerve leading to the central auditory pathway (such as auditory neuropathy) can result in sensorineural HL (Arlinger, 2007).

This thesis is focused on age-related HL, also known as presbycusis. This is the most common type of HL typically starting around middle adulthood and progressing, affecting the high frequency ranges particularly (Pearson et al., 1995; Schneider, Pichora-Fuller, & Daneman, 2010) and inducing distortion (Moore, 1995). The prevalence of age-related HL in Europe is roughly 30% for men and 20% for women at the age of 70 years, and 55% for men and 45% for women at the age of 80 years (Roth, Hanebuth, & Probst, 2001). The prevalence of age-related HL is increasing, due to populations becoming progressively older and thus presenting symptoms of reduced sensory function. A consequence of the increasing prevalence of HL is that the number of road users (not only drivers) with HL will also increase. This certainly leads to an increased need of knowledge about these individuals with regard to traffic safety and mobility.

Hearing is important for our sense of spatial orientation and temporal resolution and thus of high relevance for traffic safety. Sounds behind us provide information about events that it not possible to see and we receive information about positions and distances. Most frequency spectra of exterior tires or road noise display a prominent peak in the range of 700–1300 Hz (Sandberg, 2003). Since the noise from cars driving on roads is mainly in low frequencies, i.e., with low-pitched sounds (Wu, Stangl, Bentler, & Stanziola, 2013), individuals with presbycusis should be able to hear these specific sounds rather well. However, there might be other vital auditory input in high frequencies (e.g., a bicycle bell can be hard to hear for a pedestrian), which is partly or totally missed, and may therefore lead to loss of critical information for the listener. Distortion leads to increased difficulties in hearing masked sounds, in other words low frequency traffic noise can mask high frequency sounds. Research on effective siren characteristics suggest either a sufficiently loud, wide frequency spectrum (1–4 kHz) to overcome masking noise (De Lorenzo & Eilers, 1991; Catchpole & McKeown,

2007) or sirens that broadcast low frequencies so that the siren sound can penetrate into vehicle cabins (Howard et al., 2011). Furthermore, the use of in-vehicle systems for information, support, and navigation is rapidly increasing. These systems often use auditory signals that may not be accessible to drivers with HL. Thus, investigating other modalities such as light or vibration should be considered to also make these systems accessible to drivers with HL.

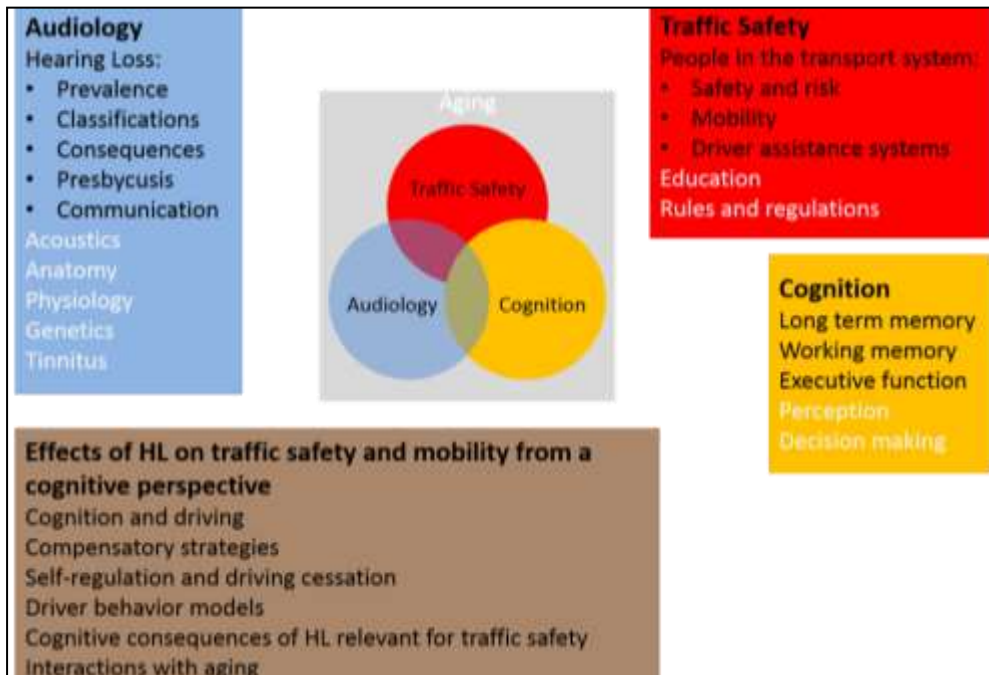


Figure 1. Overview of the thesis. The three main topics are Traffic Safety, Audiology and Cognition. These are presented and discussed separately, in relation to each other and in relation to age. Concepts included in the thesis are listed in black and terms excluded or mentioned only briefly are listed in white.

In the present thesis, traffic safety and mobility for individuals with HL is examined from the perspective of cognitive psychology. That is, how different cognitive skills in combination with HL affect traffic safety and mobility. Focus is on the intersection between three research areas: *audiology*, *cognition*, and *traffic safety*. The background and central expressions of these areas and their interrelations with each other and with age are presented in the following chapters. Figure 1 presents an overview of the thesis in terms of what is covered or excluded in each area, as well as in the intersection between them.

HEARING LOSS

The International Classification of Functioning, Disability and Health (ICF) suggested by the World Health Organization (WHO) is a framework based on the biopsychosocial model that describes the consequences of a particular health condition or disability in terms of

various levels of disablement and functioning (WHO, 2001). These may include body functions on the organic level, activities on the personal level, and participation on the social level. These levels also interact with each other and may be further influenced by personal and environmental factors. Thus, it is important to understand the consequences of a particular health condition or disability from multiple perspectives (Rimmer, 2006).

According to the ICF, functioning and disability are typically conceptualized as a complex interaction between an individual's health condition, contextual factors of the environment, and personal factors (WHO, 2001). The consequences of HL include the inability to interpret speech sounds, often producing a reduced ability to communicate, delay in language acquisition in children, economic and educational disadvantage, social isolation, and stigmatization. This may also be worsened by some medical conditions such as diabetes (Mathers, Smith, & Concha, 2003).

The degree of HL is categorized according to the better ear hearing level averaged over the frequencies of 0.5, 1, 2, and 4 kHz and divided into mild (26-40 dB), moderate (41-60 dB), severe (61-80 dB), and profound (> 80 dB) (Mathers, et al., 2003). Individuals with a HL of 95 dB or more are commonly referred to as deaf.

Age-related HL, the focus of this thesis, originates with the deterioration of auditory function and is part of normal aging, usually starting in the middle adulthood (Pearson et al., 1995; Schneider, Pichora-Fuller, & Daneman, 2010). Outer hair-cell damage, degeneration of the stria vascularis (producing endocochlear potential) and the auditory nerve are the main causes (Pichora-Fuller & Singh, 2006), and auditory processes, such as temporal resolution and duration discrimination, are negatively affected (Fitzgibbons & Gordon-Salant, 2010; Saremi & Stenfelt, 2013).

Assessment of Hearing Ability

Assessment of hearing ability is performed either psychoacoustically with an active listener (e.g., tone audiometry) or by objective methods using a physiological reaction such as electro-physical methods or otoacoustic emissions (Arlinger, 2007). Pure-tone average (PTA) is a common hearing test, relying on a patient's response to pure-tone stimuli. With PTA both air and bone conduction can be tested thus, enabling the determination of degree, type, and configuration of HL in an individual. Test frequencies begin at 1000 Hz and include at a minimum octave steps up to 8000 Hz and down to 125 Hz. Often 750, 1500, 3000, and 6000 Hz are also included. Figure 2 shows results from a PTA marked in an audiogram with test frequencies on the horizontal axis and hearing thresholds on the vertical.

COGNITION

Cognitive psychology is a necessary part for explaining human behavior. The cognitive approach is used to explain the mental processes essential for our ability to perceive and attend to, as well as memorize and communicate with, the world around us. These cognitive processes also are fundamental for our language perception, production and use, thinking, and problem solving (Eysenck & Keane, 2010). The concept 'attention' is successively being

replaced by executive functions (EFs), which are defined as a high-level process with the main obligation of adapting to new and complex situations (Diamond, 2013; Eysenck & Keane, 2010). Working memory (WM) and long-term memory (LTM) are 2 separate memory systems, which according to Baddeley (2012) are linked together by an episodic buffer working as an interface between the 2 memory systems. In order to understand the possible cognitive consequences of HL relevant for traffic safety it is important to understand both cognitive consequences of HL and road user behavior.

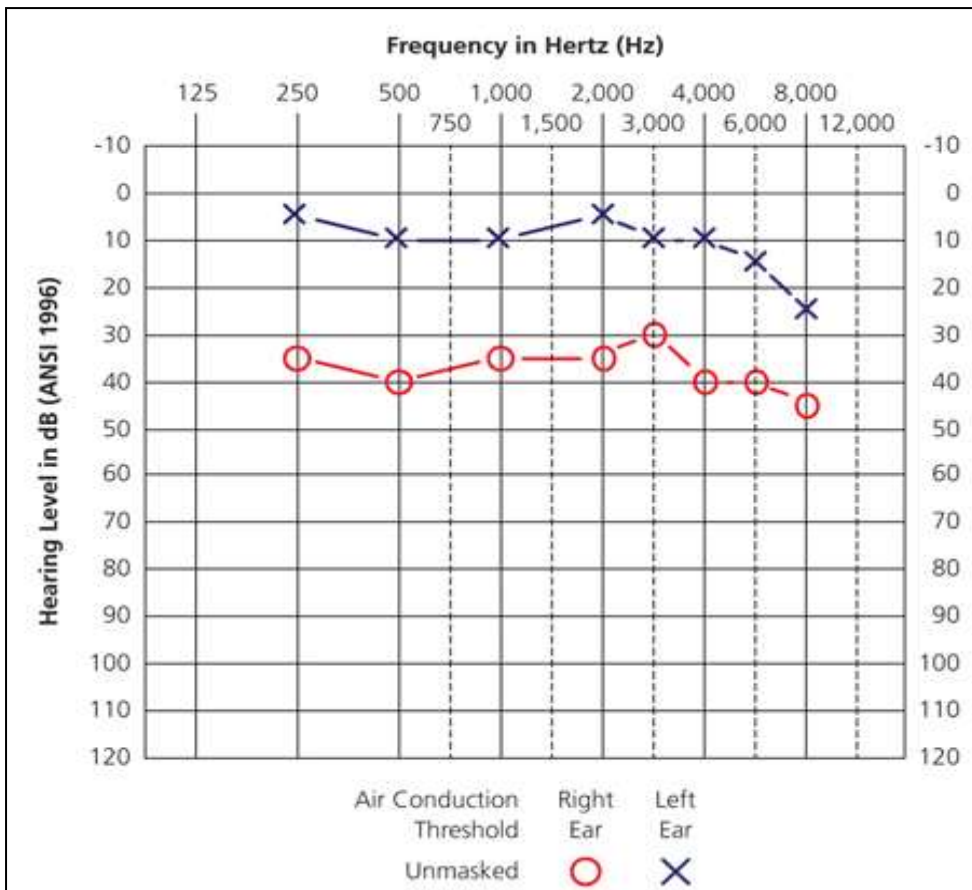


Figure 2. An audiogram presenting hearing thresholds from a PTA (air conduction).

The main focus in the present thesis is on car drivers with age-related HL. WM, LTM and EFs are involved since previous research has shown the effects of age (e.g., McDowd & Shaw, 2000; Verhaeghen et al., 2003) and HL (e.g., Andersson & Lyxell 1999; Lin et al., 2011, 2013; Rönnberg et al., 2011) on these systems. Cognitive factors such as perception and decision making is not actively examined even though effects of aging have been observed in previous studies (e.g., Johnson, 1989; Kennedy, Taylor, Reade, & Yesavage, 2010). The reason for this is the limited knowledge in this area and there is a need for constraints to be able to focus on some specific issues.

Working Memory

WM refers to a memory system with a limited capacity, and that serves to simultaneously store and process new information over a short period of time (Daneman & Carpenter, 1980; Daneman & Merikle, 1996; Miyake & Shah, 1999; Baddeley, 2012). WM is necessary in daily life in that it helps us keep things in mind when approaching a task. For example, remembering what to write down once we have found the piece of paper and a pencil or remembering what we have read once we get to the end of the sentence. In the multicomponent model of WM (Baddeley, 2012; Repovs & Baddeley, 2006) there are 4 components, each serving a specific purpose. A central executive serves as a modality independent control system, which directs and divides attention between tasks. It is involved whenever manipulation within WM is required (Repovs & Baddeley, 2006). This means the central executive controls the function of the subordinate storage components, namely: the phonological loop (dealing with language-based verbal information); the visuospatial sketchpad (processing visuospatial information); and the episodic buffer (providing a link between new and old information) (Repovs & Baddeley, 2006).

The phonological loop comprises 2 components: a passive phonological store, which holds memory traces, like speech, in acoustic or phonological form for a few seconds; and an articulatory rehearsal process linked to speech production, recoding information from other modalities (Repovs & Baddeley, 2006). According to this words and letters presented auditorily are processed differently from those presented visually. Auditory sensations have direct access to the phonological store, regardless of whether the articulatory control process is used. In contrast visual presentation of words and letters only produces indirect access through sub-vocal articulation (Baddeley, 2012; Eysenck & Keane, 2010).

The visuospatial sketchpad is dedicated to the storage and manipulation of visual and spatial information. The fourth component is the episodic buffer, which serves as an interface for binding information from different sensory sources, the other 2 subsidiary systems, and LTM. The episodic buffer also serves as an interface between perception and LTM, where the phonological and semantic representations in the lexicon are stored (Baddeley, 1983; Repovs & Baddeley, 2006). WM capacity is related to performance in most other complex cognitive tasks such as reading comprehension and problem solving (Conway, Kane & Engle, 2003). WM capacity is one reflection of individual differences in the ability to focus and maintain attention, specifically when other events are serving to capture one's attention (Kane & Engle, 2002).

In sum, WM is the ability to temporarily hold information, manipulate and use this for a special cause over a short period of time. One example from a traffic situation is a road user (driver, pedestrian or cyclist) who is about to cross the street. They must keep track of the positions of the other road users and use this information to calculate when to cross.

Long-Term Memory

LTM is a memory system where information is stored for long periods of time and remains indefinitely. In this system, declarative memory includes episodic memory and semantic memory, while non-declarative memory is divided into repetition priming and procedural memory (Eysenck & Keane, 2010). Episodic memory is the memory of personal

events (e.g., times, places, associated emotions, and other contextual knowledge) that can be explicitly stated, which is used when driving to a specific known place. The semantic LTM includes general knowledge about the world (e.g., languages, game rules, names of capital cities, authors of books, traffic rules) that the individual shares with others. The perceptual representation system recognizes items and terms, permitting rapid identification of previously encountered stimulants (perceptual or conceptual). As the name implies, procedural memory stores information on how to perform certain procedures such as walking, riding a bike and maneuvering a car (Eysenck & Keane, 2010).

Executive Functions

EFs are a set of mental processes that help us stay focused on what we are supposed to focus on (Diamond, 2013). EFs is a relatively new concept in the sense that we can relate to it more theoretically today than previously. EFs are used to perform activities such as planning, organizing, making, and using strategies, paying attention to and remembering details, and managing time and space. EFs make it possible to play with ideas, take the time to think before acting, meet novel, unanticipated challenges, resist temptations, and stay focused (Diamond, 2013). Miyake et al. (2000) defined shifting, updating and inhibiting as 3 specifically important EFs, correlated but separable. Shifting was defined by Monsell (1996) as responsible for attentional or task shifting. Updating monitors and codes incoming information according to relevance for the current task. This manipulation, instead of just storing, was described as the most important function of the updating function by Morris and Jones (1990). Miyake defined inhibition as the possibility of deliberately stopping dominant, automatic or powerful reactions and necessary to minimize distraction effects (Miyake et al., 2000).

Researchers have argued that WM capacity reflects the efficiency of EFs, especially the ability to maintain a few task-relevant representations and neglecting irrelevant information (Engle, Tuholski, Laughlin, & Conway, 1999). According to Diamond (2013), the main EFs are: inhibition, which is divided into response inhibition (self-control-resisting temptations and resisting acting impulsively) and interference control (selective attention and cognitive inhibition); WM; and cognitive flexibility (including creatively thinking outside the box, seeing anything from different perspectives, and quickly and flexibly adapting to changed circumstances).

In sum, EFs are essential in helping us in our daily life. They help us stay focused on what we are doing by updating us with relevant information and neglecting unrelated information. EFs also help us shift between tasks and think before acting, which is essential for driving a car. For example, visualization of consequences, analysis of information, and judgment of time, distance and power are necessary to be able to drive a car safely.

Assessment of Cognitive Ability

Cognitive decline is, just like HL, a part of normal aging and also related to HL (Baltes & Lindenberger, 1997; Rönnberg et al., 2011; Valentijn, van Boxtel, & van Hooren, 2005). Therefore, it is important to control for differences in cognitive abilities when comparing

driving performance between a group with HL and a group with NH. This can be accomplished by cognitive testing.

WM Capacity

There are several tests designed to evaluate WM capacity. A commonly used measure is a dual-task paradigm combining a memory span measure with a concurring processing task. Daneman and Carpenter (1980) invented the first version of this kind of task, called the “reading span test”. In their test participants read a number of sentences (usually between 2-6) and tried to remember the last word of each sentence. At the end of the list of sentences, they tried to repeat back the words in the correct order. Individual WM capacity, as measured by the reading span test (Andersson, Lyxell, Rönnerberg, & Spens, 2001; Daneman & Carpenter, 1980; Rönnerberg, 1990), has shown to account for 40% of the inter-individual variance of speech recognition in noise among participants with similar levels of HL (Lunner, 2003).

Impairments in visuospatial ability (measured by, for example, copying the wire cube, pentagons, drawing a clock face) are good markers of increased driving risk (Kipps & Hodges, 2005). The clock drawing test (CDT) is a simple tool that is used to screen people for signs of neurological problems such as Alzheimer’s and other dementias. CDT assesses primarily EFs by letting the participant draw a clock with hands pointing at a specific time.

TIPS (Text Information Processing System, Ausmeel, 1988), is a cognitive test platform developed according to established cognitive models of WM, phonological and lexical ability (see Baddeley, 2012; Abreu, Gathercole, & Martin, 2011; Shah & Miyake, 1996). The battery intends to measure WM capacity, phonological abilities and lexical abilities, and thus includes several tests for each of these cognitive aspects. A shorter computer-based version of TIPS was developed for use in clinics. Both this and TIPS have been used in a large number of studies (e.g., Hällgren, Larsby, Lyxell, & Arlinger, 2001, Bergemalm, Hennerdal, Persson, Lyxell, & Borg, 2009; Lidestam, Lyxell, & Andersson, 1999; Hua, 2014). The reading span test aims to measure the WM capacity. Two tests include reaction time measure of phonological ability (deciding whether 2 letters are identical and deciding whether 2 words rhyme).

Processing Speed, Divided Attention, Selective Attention

Skills measured by Useful Field of View (UFOV) are used during driving (Ball & Owsley, 1993), and the test is intended to be indicative of accident risk in the older population (Ball, Owsley, Sloane, Roenker, & Bruni, 1993; Owsley et al., 1998). In the first subtest, measuring processing speed, the participant is asked to identify which vehicle (car or truck) is displayed on the screen for a short time. In the second subtest, evaluating divided attention, the participant should, in addition to the first task, localize a car placed in the periphery on the screen. The third subtest, assessing selective attention, is identical to subtest 2 but with the rest of the screen filled with distracting triangles.

The trail-making test (TMT) assesses visual search, processing speed and mental flexibility (Reitan, 1986). Part A consists of targets marked with numbers, which are connected in numerical order, and part B are targets marked with both numbers and letters, which are connected in a combined numerical and alphabetical order such as 1-A-2-B-3-C and so on. On a computerized version of TMT developed by Summala et al. (2008), the target locations are fixed on the screen but the content, that is numbers or letters, are either the same

(fixed) or randomly changed after each tap on a touch screen instead of the traditional pen and paper version.

Hearing Loss, Cognition and Aging

Commonly, when talking about older people, older adults and elderly, this refers to individuals over the age of 65 (Gordon-Salant, 2005; Gorman, 1999; Roebuck, 1979). This also applies for this present thesis. Numerous studies have shown that there is a correlation between HL and cognitive decline in old age (Granick, Kleban, & Weiss, 1976; Thomas, Hunt, Garry, Hood, Goodwin, & Goodwin, 1983; Lindenberger & Baltes, 1994; Baltes & Lindenberger, 1997; Li & Lindenberger, 2002; Lin, Ferrucci, Metter, An, Zonderman, & Resnick, 2011; Rönnberg et al., 2011), which will be presented more specifically in a subsequent section.

Because age-related HL is the most common type (Roth, Hanebuth, & Probst, 2001; WHO, 2001), it is important to understand other consequences of normal aging, which more or less affect or are affected by HL. For example, the deterioration of auditory functions such as like speech understanding is worsened by age-related changes in the cognitive system (Grady, 2012; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Older adults with NH have also shown more difficulties with speech recognition than younger individuals with NH (Frisina & Frisina, 1997; Gordon-Salant, 2005), which can, for example, affect the possibility of using auditory-based driver assistance systems.

Cognitive Consequences of Aging

Aging is associated with the decline in the control processes involved in coordinating distinct tasks such as reaction times, WM tasks, tests of episodic memory, tests of spatial and reasoning abilities, mental rotation, and visual search performance (McDowd & Shaw, 2000; Verhaeghen et al., 2003). However, on specific vocabulary tests, no effects of age have been shown, for example by Elliott et al. (2003) using the Wechsler Adult Intelligence Scale Vocabulary subtest (Jastak & Jastak, 1964) and by Bowles and Salthouse (2009) using multiple-choice synonyms, multiple-choice antonyms and produce-the-definition.

The effects of aging have also been demonstrated when switching between specific tasks (e.g., switching between responding to color or form and responding only to color, Mayr et al., 2001; Verhaeghen et al. 2005), and are also related to attention (Craik & Salthouse, 2000; Phillips & Lesperance, 2003). Slower cognitive processing is also associated with aging (Cerella, 1990; Salthouse, 1996) and it is estimated that processing takes 1.5-2 times longer in older than in younger adults (Cerella, 1990). This affects most age-related declines in performing complex cognitive tasks such as problem solving, reasoning and language comprehension (Salthouse, 1996; Verhaeghen et al., 2003).

Aging is also associated with reductions in WM for both processing (van der Linden et al., 1994, 1999; Bopp & Verhaeghen, 2005) and capacity (Bopp & Verhaeghen, 2005; Salthouse & Babcock, 1991). Specifically, the episodic memory of LTM is negatively affected by age while semantic memory remains relatively stable or may even increase, and

on the non-declarative memory no conclusive aging effect has been shown (Brickman & Stern, 2009).

Some of these age-related cognitive declines can be of major importance for safe mobility (e.g., reaction times, visual search performance, processing speed, problem solving), specifically for driving, which according to Groeger (2000) is one of the most complex and safety critical everyday tasks in modern society.

Cognitive Consequences of HL

Specific and general effects of HL on cognitive functions have been demonstrated (e.g., Andersson, 2002, Lin et al., 2011, Rönnberg et al., 2011). For example, a relationship between severe to profound HL and deficiency in certain aspects of phonological processing has been demonstrated and suggested to come from a gradual loss of specificity of phonological representations (Andersson, 2002; Andersson & Lyxell 1999; Lyxell, Andersson, Borg, & Ohlson 2003; Rönnberg et al., 2011; Classon, 2013). Andersson (2002) concluded that specific aspects of the phonological system deteriorate in the HL population as a function of auditory deprivation. In particular, the phonological representations are impaired and this impairment also affects the ability to rapidly perform phonological operations.

HL has been demonstrated as independently associated with accelerated cognitive decline (30-40%) and incident cognitive impairment (24%) among older adults during a six-year period. (Lin et al., 2011). These effects have been shown with the Modified Mini-Mental State test (Teng & Chui, 1987), which is a verbal cognitive test, as well as with a non-verbal cognitive test (called Digit Symbol Substitution, Wechsler, 1981), in both cross-sectional and prospective studies (Valentijn et al., 2005; Peters, Potter, & Scholer, 1988). Specifically, verbal tests have shown the relationship between HL and cognitive decline more extensively than non-verbal tests (Granick et al., 1976; Thomas et al., 1983).

The more general effects of HL on cognitive functions may affect traffic safety more and are in line with Baddeley (2012), who found that articulatory suppression leads to WM decline. Prospective studies have found accelerated cognitive decline and increased risk of dementia and Alzheimer's in individuals with HL (Lin et al., 2011, 2013). Cross-sectional studies have shown that HL is associated with lower performance in tests of EFs and free recall (Lin, 2011) and has a negative effect on episodic and semantic LTM (Rönnberg et al., 2011). With a decline in WM, EFs and LTM, it might, for example, be more difficult to stay focused on the driving task, keep track of the surrounding traffic or to remember traffic rules.

Another aspect worth considering is cognitive fatigue, due to higher effort in listening, leading to decreased cognitive capacity. This effect has been shown on both young and adult listeners with HL (Arlinger, 2003; Hicks & Tharpe, 2002; Tun, McCoy, & Wingfield, 2009). In addition, several studies have shown that hearing aids do not fully restore speech difficulties of individuals with HL (e.g., Dimitrijevic et al., 2004; Moradi, Lidestam, Hällgren, & Rönnberg, 2014; Nakeva von Mentzer, 2014), which made perceiving speech stimuli cognitively demanding (Moradi et al., 2014; Rönnberg et al., 2013).

This cognitively demanding processing of speech stimuli may increase fatigue in individuals with HL during conversations with their partners while they are driving. Cognitive fatigue could, among other things, lead to decreased attention and thus be relevant

to traffic safety. Moreover, mobility might be affected if cognitive fatigue leads to decreased driving.

Furthermore, dual sensory decline (hearing and vision) is associated with cognitive decline and for a functional decline on everyday activities over a period of 4 years (Lin, Gutierrez, & Stone et al., 2004). Thus, research questions with regard to age-related HL and traffic safety require the combined study of several factors associated with declines due to aging.

In sum, specific cognitive declines of HL have been demonstrated and include, for example, phonological deficiencies (processing and representation) as a consequence of less auditory stimulation (specificity of phonological representations). Traffic safety might be affected due to a decline in WM, EFs and LTM, which can lead to difficulties to stay focused on the driving task, keep track of the traffic around or to remember traffic rules. Also, cognitive fatigue could lead to decrease in attention and thus be of relevance for traffic safety.

Cognition and Traffic Safety

Groeger (2000) described driving a car as one of the most complex and safety critical daily tasks in modern society (Groeger, 2000). Driving is a cognitively motivated and controlled task. When demands are high, driving is carried out in a force-paced way, while when the demands are low, in a more self-paced way (Peters & Nilsson, 2006). Thus, workload is an aspect of driving that should be considered, and in this thesis the term *cognitive workload* is used, when others might be using *mental workload*. De Waard (1996) defined driver workload as the individual reaction to driving task demand and further refers to Rouse et al., who defined experienced load, which is not only task-specific but also person-specific. (Rouse Edwards, & Hammer, 1993).

More specifically, workload is the specification of the amount of information processing capacity that is used for task performance. Therefore, workload depends on the individual, and owing to the interaction between operator and task structure the same task demands do not result in an equal level of workload for all individuals (de Waard, 1996).

Directly related to driving task demand is task complexity. According to de Waard (1996), complexity increases with an increase in the number of stages of processing that are required to perform a task. Task demand and complexity are mainly external, but both depend on subjective goals set for task performance. Difficulty of a task is related to the processing effort that is required by the individual for task performance, and is dependent on context, state, capacity, and strategy or policy of allocation of resources (de Waard, 1996).

Driving effort is dynamic, as the cognitive demands can change back and forth from very low to extremely high, sometimes within fractions of a second (Michon, 1985; Peters & Nilsson, 2006). Among the factors determining the driving task demand, of which the driver has immediate and direct control, driving speed is the most significant (Fuller, 2005). It has been demonstrated that when a threshold of a certain preferred driving speed is exceeded, experienced task difficulty, effort and feeling of risk is affected (Lewis-Evans, 2011).

In sum, driver workload is the individual reaction to driving task demand, which is directly related to task complexity. Task demand and complexity changes back and forth due to external circumstances and subjective goals, which makes the driving task and driver

workload very dynamic. Feelings of risk arise when the task complexity goes above a certain threshold.

Driver Behavior Models

An advance within traffic behavioral research has been the increased understanding of the driving task from a cognitive perspective, and consequently the skills needed for carrying out this task successfully and safely. Since perceptual and psychomotor abilities are essential to model driving behavior, driving can be viewed as a cognitive task of control in a context perceived through the senses and manipulated with control actions based on unconscious (automated) or conscious decisions (Peters & Nilsson, 2006).

Carsten (2007) distinguishes between 2 broad types of driver models. The first type is descriptive of parts or the whole of a driving task in terms of *what the driver has to do* and includes, for example, task models (Michon, 1985; McKnight & Adams, 1970), adaptive control models (McRuer et al., 1977; Hollnagel et al., 2003), and production models (Michon, 1985). Michon (1985) described driving a car as a complex task with processes at a minimum of 3 hierarchical levels. At the top level, the strategic level, strategic decisions are made such as the choice of means of transport, setting of a route goal, and route-choice while driving. At the intermediate level, the maneuvering level, reactions to local situations, including reactions to the behavior of other traffic participants, take place. Basic vehicle-control processes, such as lateral-position control, occur at the lowest level, the control level. At this level automatic processes occur, while at higher levels higher controlled processing is required.

The second type is motivational models, aiming to describe *how the driver manages task difficulty*. In contrast to the descriptive models, sometimes being merely descriptive or analytical, motivational models attempt to explain which psychological factors affect driver behavior and why drivers make certain decisions (Michon, 1985).

According to Ranney (1994), errors associated with the variability of human behavior may be more important to roadway crash causation than systematic errors, which are attributable to the known limits of the human information-processing system. Furthermore, given the ever-increasing variety of driving situations, including changes in the driving task associated with different technologies, and the corresponding variety of skills and abilities required, Ranney (1994) claimed it unlikely that a comprehensive model of driver behavior will ever be feasible.

For the purpose of this thesis, we expect that differences related to HL are not as likely to occur in terms of what the driver has to do, but rather may occur in the management of task difficulty and when making certain decisions. Therefore, motivational driver behavior models will be presented and discussed in more detail from the HL perspective.

Motivational Models

The most well-known motivational model is Wilde's (1982) Risk Homeostatis Model (RHM), introducing the notion of driver capability affecting risk (Carsten, 2007). Wilde proposed that there is a preferred target level of risk of being involved in an accident that drivers seek to maintain. Fuller and Santos (2002) proposed the Task Difficult Homeostasis (TDH) (see also Fuller, 2005, 2007; Fuller et al., 2008; Fuller, McHugh et al., 2008), stating that people have a set range of experienced task difficulty at which they prefer to operate. TDH was then re-conceptualized into Risk Allostasis Theory (RAT), where the acceptable

range of task difficulty is accompanied by and essentially interchangeable with a range of preferred feeling of risk (Fuller, 2008; Fuller, 2011).

The Risk Monitor Model (RMM) (Vaa et al., 2000; Vaa, 2003, 2007, 2011) suggests that all individuals have a drive to maintain or obtain a target best feeling, which is variable in both its value and the type of feeling, however, including, for example: tension or anxiety, arousal, sensation, pleasure, relaxation, difficulty avoidance, compliance, and non-compliance (Vaa, 2007).

The Multiple Comfort Zone model (MCZ) by Summala (2005) is an evolution of the earlier zero-risk theory (Näätänen & Summala, 1974). Being a motivational model it views a driver's excitatory motives, personality and driving goals as prevailing factors. These motives interact with the road system and push drivers toward changing their behavior to satisfy their driving goals, for example by increasing speed to arrive at a destination on time (Summala, 2005; Summala, 2007).

What the presented motivational models all have in common is the level of risk, and it is suggested that the driver aims at maintaining this level. Whether drivers with HL are at higher risk than NH drivers or not is uncertain since there are studies suggesting connections between HL and higher risks of traffic accidents (Ivers, Mitchell, & Cumming, 1999; Picard et al., 2008) and also research where no such relationship has been found (Green, McGwin, & Owsley, 2013; McCloskey, Koepsell, Wolf, & Buchner, 1994). However, if there is a difference in risk related to HL there should, according to the motivational models, also be a different level of risk in which the drivers with HL aim to maintain. This could be driving at a lower speed, for example.

Lewis-Evans (2012) experimentally tested 4 motivational models of driver behavior: TDH, RAT, RMM, and the MCZ (Summala, 2005; Summala, 2007). He concluded that the speed is not solely a conscious choice but handled, at least at some difficulty level, by automatic processes, and that the existence of these processes can be inferred when the cognitive capability of drivers is put to the test. Furthermore, results from the experiments supported the idea of a threshold to account for the perception of subjective variables such as task difficulty, effort, comfort, crash risk, and feeling of risk. For predicting difficulty of the task, the variables that the participants were most sensitive to changes in were speed and following distance. Lewis-Evans (2012) claims that these findings support models such as the MCZ (Summala, 2005; Summala, 2007) due to the reliance of this model on actual performance measures in driving such as time to line crossing or time to collision.

In line with Lewis-Evans' findings are the results from Lidestam, Lundqvist and Rönnerberg (2010), who tested the external validity of theoretical driver behavior models by letting traffic inspectors rate the importance of theoretical concepts found in research literature on risk awareness. It was revealed that visual search was the most important concept, and that the assessment of risk awareness can be conceptualized as assessment of lower-order (maneuvering and position, cf. Michon's control level) and higher-order (attention, traffic behavior and speed, cf. Michon's manoeuvre level) cognitive functions.

In sum, according to motivational driver behavior models, drivers aim to maintain a preferred level of risk. The results in Lewis-Evans (2012) with regard to speed and following distance suggest time-based safety margins as relevant measures of this individual level of risk, and visual search is proposed as a valid indicator of risk awareness (Lidestam et al., 2010). This is all in line with Gibson and Crooks' very first model of driver behavior: field of safe travel (Gibson & Crooks, 1938). All of this is relevant for understanding the effect of HL

on driving behavior and for the evaluation of driver support systems. Recurring in the models is the driving speed, and several studies have linked speed perception to the amount of noise in car cabins or to the driving sound (Evans, 1970; Ohta & Komatsu, 1991). Thus, speed might be perceived differently by drivers with hearing loss, due to a reduced sensitivity to sounds.

TRAFFIC SAFETY

One goal of traffic research should be to provide the safest possible mobility for all road users, regardless of their levels or types of abilities or disabilities. In all motivational models presented above, drivers aim to maintain a preferred level of risk, above a certain threshold. Whether drivers with HL are at higher risk than NH drivers is uncertain because previous findings are contradictory. For example, some studies found increased risk for drivers with HL (Ivers, Mitchell, & Cumming, 1999; Picard et al., 2008), while others did not (Green, McGwin, & Owsley, 2013; McCloskey, Koepsell, Wolf, & Buchner, 1994).

According to Rumar (1988), there is always a risk in being mobile, and he divided risk into statistical (objective) risk and experienced (also called subjective or perceived) risk. For drivers with HL, research results are limited and rather contradictory on objective risk, and we found no results on subjective risk in our extensive literature surveys. Thus, it might be that drivers with HL can experience a subjective risk even if there is no objective risk. Research results so far do not identify clearly increased objective or subjective risks for drivers with HL, but this might be due to lack of knowledge. Therefore, there may be no increased risk at all for drivers with HL; there might be a small and unimportant risk; or there could be an important increased risk research has yet to reveal.

The level of knowledge on the relationship between HL and statistical traffic safety is relatively low and too inconsistent to draw any conclusions. Crash data have shown that drivers with HL are at higher risks of traffic accidents (Ivers, Mitchell, & Cumming, 1999; Picard et al., 2008). However, there is also research on crash data and medical record data where such relationships have not been found (Green, 2013; McCloskey, Koepsell, Wolf, & Buchner, 1994). On the effect of HL on subjective traffic safety the literature is even scarcer. Lundälv (2004) found that adult pedestrians and cyclists with moderate HL had no self-reported experiences of feeling insecure in the traffic environment; however, he also suggested that these individuals are at higher risk of being injured by a vehicle because they report that they find it difficult to identify the direction sounds come from.

While traffic safety and mobility for drivers with HL is almost unexplored, the research literature regarding older drivers is relatively extensive. With age-related HL being the most common type (Roth, Hanebuth, & Probst, 2001; WHO, 2001), the effects of age are very relevant and will be discussed further in the following sections, along with the possible effects of HL.

Mobility and Quality of Life

Transportation is a part of everyday life and may be necessary for participation in activities and social life. Several studies suggest that travel habits will further increase for older adults in the future (Dillén, Schmidt, & Jarlebring, 2005; Hausten et al., 2013; Hjorthol, Levin, & Sirén, 2010) and this is explained by attitudinal effects (higher mobility needs, more active lifestyles), improved physical possibilities (fitness and health conditions), and cohort effects (being born at about the same time, exposed to the same events in society, and influenced by the same demographic trends and thus having similar experiences; Hausten, 2013).

In this thesis, mobility refers to the quality or state of being mobile - the ability to move freely. The ICF model includes mobility in activity and participation. Several studies have proven that limitation of activities increase with the degree of HL (Gopinath, Schneider, Hickson et al., 2012; Grue et al., 2009; Wallhagen et al., 2001; Schneider et al., 2010). HL has also been found to affect instrumental activities such as talking on the telephone or using public transportation more than daily activities such as getting dressed or eating (Gopinath, Schneider, McMahon, et al., 2012).

Car access is associated with better health and well-being among the elderly (Ellaway, Macintyre, Hiscock, & Kearns, 2003; Macintyre, Hiscock, Kearns, & Ellaway, 2001). By enabling older people with physical limitations to still live independently and to participate in normal daily activities, the car can act as a compensational tool for functional limitations (Sirén & Hakamies-Blomqvist, 2004, 2009). According to Köpke, Deubel, Engeln and Schlag (1999), car availability and car use are related to positive self-perception in older people, and research suggests driving cessation may be a risk factor for a depressive development (Fonda, Wallace, & Herzog 2001; Marottoli et al., 1997). With age-related HL being the most common type of HL (Pearson et al., 1995; Schneider, Pichora-Fuller, & Daneman, 2010) and with increasing travel habits among older adults (and the gap between actual mobility and desirable mobility), it is important to understand the effect of HL on mobility.

Self-regulation of driving usually refers to the voluntary reduction or avoidance of certain (typically challenging or demanding) driving situations (Hausten, 2013). This could also be a way of maintaining the level of risk by not exposing oneself to specific traffic situations. Factors found to be associated with self-regulation of driving are functional decline, and increasing cognitive and visual restrictions (Ball et al., 1998; Charlton, Oxley, Fildes, Oxley, & Newstead, 2003; Holland & Rabbit, 1992), and one's perceived driving skills (Gabaude, Marquié, & Obriot-Claudel, 2010; Rimmö & Hakamies-Blomqvist, 2002).

The most common medical conditions affecting driving cessation include sensory problems, cognitive impairment, stroke, cardiovascular, and other heart conditions, diabetes, and physical mobility and activity problems (Brayne et al., 2000; Dellinger, Kresnow, White, & Sehgal 2004; Forrest, Bunker, Songer, Cohen, & Cauley, 1997; Hakamies-Blomqvist & Wahlström, 1998). Edwards et al. (2009) indicated that driving cessation is associated with declines in physical and social functioning, as well as in general health (Edwards, Lunsman, Perkins, Rebok, & Roth, 2009).

In sum, various age-related declines are associated with self-regulation and driving cessation. Because car access is associated with better health among the elderly, it is important to assist driving for older adults when possible. One way of achieving this is to ensure that driver assistance systems are also accessible for drivers with HL.

Effects of Aging on Driving Behavior

Factors associated with old age and that have a negative impact on the ability to drive include impaired perceptual abilities, memory decline, reduction in the ability to sustain and switch attention, and mobility constraints (Groeger, 2000). However, aging is usually a gradual process and while some skills deteriorate with increasing age, others (more strategic) are used more with increasing age (Haustein, 2013).

As car drivers, older persons perceive certain driving situations and conditions as demanding and potentially dangerous. These include driving in specific weather conditions (e.g., fog, rain or a storm), when feeling physically unwell or excited, in high traffic density, on specific road types (e.g., motorways or highways), on roads with certain characteristics (e.g., signals, traffic lights, curves, roundabouts), and in response to others' driving behaviors (e.g., tailgating) (Jansen et al., 2001; Sullivan, Smith, Horswill, & Lurie-Beck, 2011).

Compensatory strategies addresses the regulation of loss as a function of aging or disability (Riediger, Li, & Lindenberger, 2006; Lindenberger, Lövdén, Michael Schellenbach, Li, & Krüger, 2008). It involves efforts (consciously or unconsciously) to maintain a given level of functioning despite decline in, or loss of, previously available resources (Riediger, Li, & Lindenberger, 2006; Lindenberger, Lövdén, Michael Schellenbach, Li, & Krüger, 2008; Donorfio, Mohyde, Coughlin, & D'Ambrosio, 2008; Haustein et al., 2013; Monterde-i-Bort, 2004). Compensation, in contrast to optimization, aims at counteracting or avoiding losses rather than achieving higher levels of functioning (Riediger, Li, & Lindenberger, 2006). When driving, compensatory strategies could be a way to maintain the level of risk as described in the driver behavior models.

Older drivers often show a more defensive driving style with lower average speeds (Chipman, MacGregor, Smiley, & Lee-Gosselin, 1992; Haustein et al., 2013) and keep a larger following distance (Rajalin, Hassel, & Summala, 1997). Age-related changes in driving patterns can be seen as a strategy to compensate for age-related decline and thus prolong the period of independent safe mobility (Donorfio et al., 2008).

In psychology, coping refers to the use of conscious effort to solve personal and interpersonal problems, seeking to master, minimize or tolerate stress or conflict (e.g., Ben-Zur, 2009; Carver & Connor-Smith, 2010). One way of coping can be to simply avoid situations that cause stress or discomfort. Older drivers have been found to choose not to drive in certain conditions or environments and avoid risk-taking (Haustein et al., 2013). Driving conditions avoided by older drivers include rush hours, darkness, poor weather or road surface conditions, driving in unfamiliar areas (D'Ambrosio et al., 2008; Gwyther & Holland, 2012; Hakamies-Blomqvist, 1994; Rothe, 1990). Moreover, older drivers are less likely than middle-aged drivers to be engaged in distracting activities such as adjusting in-vehicle equipment or using a mobile phone (Fofanova & Vollrath, 2012; McEvoy, Stevenson, & Woodward, 2006). Avoidance of distracting activities while driving is one coping strategy.

To summarize, the ability to drive is affected by the deficits that come with age and lead to changes in driving behaviors. The behavioral patterns of older drivers are more cautious and include both compensatory strategies (e.g., lower speed, longer distance) and coping strategies (e.g., avoidance of certain situations or distracting activities).

Assessment of Driver Behavior

According to de Waard (1996), good reflectors of primary-task performance at the control level (c.f. Michon, 1985) are measures of lateral position (LP) and steering wheel (SW) movements and at the maneuvering level (c.f. Michon, 1985) include the time-to-line-crossing (TLC; Godthelp, 1984). Standard Deviation Lateral Position (SDLP) has been shown to be a sensitive performance measure (e.g., Hicks & Wierwille, 1979, O'Hanlon et al., 1982, O'Hanlon, 1984). De Waard (1996) showed that increased road complexity could lead to an increase in the SD of the SW movements, while the addition of a secondary task reduced the SD of the SW movements. Manipulation of both driving speed (e.g., Fuller, 2008; Summala, 2007; Levis-Evans, 2012) and degree of engagement in secondary tasks (Fuller, 2005) may be most important in maintaining the preferred level of risk.

Visual-search strategy has been shown to be indicative of informational needs (Hughes & Cole, 1988). According to de Waard (1996), eye-tracking measures are related to primary-task performance; however, they can also be used as a secondary-task performance measure in the case of embedded tasks. This is how eye tracking was used in the experimental studies in the present thesis. In the simulator study, driving was the primary task and an additional device was used for the secondary task. In the field study, drivers had to look at the navigation display to know which way to go. Relationships between frequency of fixation and instrument importance, as well as between length of fixations and difficulty in obtaining information from instruments, have been shown by Wilson and Eggemeier (1991). O'Donnell and Eggemeier (1986) reported that an increase in workload was accompanied by an increased fixation time.

Advanced Driver Assistance Systems

One approach to accident prevention and injury reduction is the introduction of in-vehicle-based preventive safety functions, also known as Advanced Driver Assistance Systems (ADAS) (e.g., lane-keeping support, adaptive cruise controllers, collision warning systems). In contrast to protective, or passive, in-vehicle safety functions (e.g., seat belt, airbag), whose purpose is to mitigate crash consequences, the general goal of ADAS is to prevent crashes from occurring at all. This is meant to be achieved either by alerting the driver to potential hazards (warning) or by taking over the driving task to some extent (intervention), using, for example, autonomous braking in emergency situations (Ljung Aust, 2012). Carsten and Nilsson (2001) made the distinction between information systems, that interact with the driver, and other intervening systems, that interact directly with the vehicle. Navigation systems are typical of the former category and adaptive cruise control of the latter.

An ADAS typically consists of one or more environment sensors mounted on the vehicle, for example radars or cameras. Software that uses sensor input determines what actions the ADAS should take and the particular driver or vehicle interface is used to alert the driver or control the vehicle. Examples of safety technologies, which fall under the ADAS umbrella, are Forward Collision Warning (FCW), Adaptive Cruise Control, Lane Departure Warning, and Drowsiness Warning (Ljung Aust, 2012).

A key issue for ADAS systems is to verify that they actually improve traffic safety. While the safety potential of ADAS can be affected by many factors, Carsten and Nilsson

(2001) proposed that all safety implications can be classified as belonging to either of three general aspects: the function safety aspect (technical reliability of the system); the Human Machine Interaction (HMI) aspect (operating, and communicating with, the system); and the traffic safety aspect (system influence on driving behavior, including changes in interactions with other road users).

Relevant for both the HMI aspect and the traffic safety aspect is the multiple resource theory (MRT) presented by Wickens and Hollands (1999). This theory describes information processing with stages (perception, WM and cognition, responding), modalities (visual, auditory) and codes (verbal, spatial). An important implication of the difference between processing codes is the ability to judge which control to use for response. Manual control may reduce performance if there are heavy demands on spatial working memory, for instance while driving, whereas voice control may disturb the performance of tasks with heavy verbal demands (Wickens & Hollands, 1999).

The HMI aspect is central to the effect of HL on the use of driver assistance systems, since communication with the system must be set such that NH is not crucial, meaning that output cannot be only auditory. Several studies have shown that tactile support is an intuitive and effective way of presenting direction information and alerting drivers to potential collisions (van Erp & van Veen, 2004; Ho, Tan, & Spence, 2005; Ho, Reed, & Spence, 2006). From the traffic safety aspect, this may release other heavily loaded sensory channels and therefore potentially provide a major safety enhancement.

Another issue is whether there are effects of HL on driving behavior. Concerning the fact that most HL is age-related, Li and Perkins (2007) showed that seniors view technology in the same way as the general public, and that education has a larger influence on the willingness to learn about new technology than age does. For training, simulators can be used to provide hands-on experience of new driver support systems and may therefore be valuable supportive tools for the elderly driver (Peters & Nielsen, 2007).

In sum, ADAS aim to increase traffic safety by preventing crashes. To make the systems accessible for drivers with HL, alternatives to auditory signals are necessary. Tactile signals have been shown to be effective and intuitive in warning and providing directional information.

GENERAL AIM AND RESEARCH QUESTIONS

The general aim of this thesis is to investigate traffic safety and mobility for individuals with HL from a perspective of cognitive psychology by using subjective and objective performance indicators. With the limited previous research and knowledge on this specific topic, the approach has been necessary exploratory. Three studies were conducted: a questionnaire survey and two experimental studies, whereof one driving simulator study and one field study. The overall aim of the questionnaire study was to evaluate whether there were any differences related to HL with regard to the choice of transportation or on the view of hearing in transport situations. With the limited previous knowledge in the field, there were no expected differences between the groups. The studies following the questionnaire study had more specific research questions and expectations. Henceforth, the population included in

the studies was older adults, in order to create homogenous groups and also because the majority of HL is age-related.

Based on the results from the survey, the driving simulator study was conducted to examine if HL had an effect on driving behavior or on increased workload. Gaze data was analyzed to compare visual behavior and in addition, the efficiency of a tactile signal to alert the driver was evaluated. A more cautious driving behavior was expected among the drivers with HL, because of compensatory strategies such as longer distance to other vehicles, lower driving speed and a more active visual search behavior. Coping strategies such as paying less attention to the secondary task were also expected.

A field study was conducted to replicate and validate the effects from the simulator study in real traffic. In the field study, the aim was to also evaluate a driver assistance system (navigation system) with a supportive tactile signal. Compensatory strategies such as slower driving speed and more glances in the mirrors were expected for the drivers with HL. The tactile support was expected to lead to more focus on the road, better driving performance and higher satisfaction with the system.

METHODS

Ethical Considerations

In the studies presented in this thesis, the aim was to create as homogenous groups as possible with regard to age-related HL, and to control for vision loss and cognitive decline. Ethical considerations mainly concerned integrity issues (no data could be tracked back to any individual). Potential ethical problems identified in the studies include missing or lacking information with regard to the aim of the studies, the optional participation (participants could resign at any time without having to give any motive), the noncompulsory sharing of personal audiograms, and the receipt and treatment of the audiograms. All of the studies presented in this thesis were conducted during 2011-12 in Linköping and received ethical approval from the Research Ethics committee (Etikprövningsnämnden, EPN 2011/125-31; 2012/345-31) in Linköping.

Methodological Challenges

There were three different assessments to evaluate the effect of HL on traffic safety and mobility: the assessment of HL; the assessment of cognition, and the assessment of traffic safety each challenging and each with several possible methods. The results from each assessment were then to be put in relation to the other 2, which was even more challenging. Some of these challenges are presented in this section.

HL Population and Recruitment of Participants

Individuals with HL constitute a heterogeneous population due to a large variation in age, level of HL, and onset and cause of HL. Additionally, HL may be either unilateral or bilateral. This heterogeneity, in combination with the low level of knowledge in the area of HL and

traffic safety, makes designs with sharp hypothesis-testing difficult to conduct. However, the population is large and thus, for the experimental studies and from a heterogeneous population included in the questionnaire study, we recruited as homogenous a group as possible. This was sensible and realistic, and provided a perspective based on the reality of those living with HL.

Geographical differences and variations in driving experience had also to be considered. Traffic situations may be very different in large cities and small towns, and individual driving experience may affect how people cope with any particular situation. However, in the studies included in this thesis, all participants were recruited from the same region and at least mileage per year and years with a driver's license was controlled for.

As well as HL, loss of vision is also a part of normal aging (e.g., Risacher et al., 2013; Heyl & Wahl, 2012). Wearing glasses can cause problems with eye tracking (Eachus, Cassidy, Norgate, Marrow, & Greene, 2008; O'Brien & Sharon, 2009), and this consideration restricted our potential participants. Furthermore, there will always be uncertainty of the representativeness of participants in any study. Not all individuals are willing to take part in research studies, and there is a risk that whatever characterizes those willing to participate from those not willing will lead to systematic sampling errors.

Response rate and completeness of questionnaires are difficult to control when participation is voluntary. There are arguments for and against using Internet (electronic) or paper and pencil versions. One advantage of electronic versions, besides the efficiency of receiving all answers in a database, is the opportunity to control that all questions have been answered before submission. However, paper versions have been found to have a higher response rate than electronic versions (73.2% compared to 17.9%, respectively) (Kongsved, Basnov, Holm-Christensen, & Hjollund, 2007).

Driving Simulator Versus Real Driving

The advantages of performing simulator studies, including the opportunity to offer a safe convenient alternative to measuring driving performance on the road and the ability to keep driving conditions and environmental conditions constant, also come with limitations (Mullen, Charlton, Devlin, & Bédard, 2001; Nilsson, 1993). For example, motion, velocity and acceleration ranges are limited. It is impossible to fully represent a real traffic environment, and there is also the chance of simulator sickness, a type of motion sickness specifically experienced in simulators (Nilsson, 1993). Moreover, the simulated world does not contain the same level of detail and roughness as the real world. Since there is a limited amount of details in the simulated world, there is also less to focus on. It is not known how much this limitation affects visual behavior. Simulator performance shows medium to strong correlations with many on-road driving performance measures, and with other cognitive and physiological measures. However, simulators must be validated for each new setting (Mullen et al., 2001).

Challenges with Cognitive Assessments

One of the greatest concerns when creating a test for cognitive assessment is whether or not it actually measures what we think it is measuring. A test has construct validity if it demonstrates an association between the test scores and the prediction of a theoretical characteristic. Hughes, Sapp, and Kohler (2006) presented the challenges of conducting accurate cognitive assessments of students with HL. The authors pointed out that poor

performance on an assessment may not necessarily indicate lower ability, but may be the result of a misunderstanding of the type or language of the assessment. Thus, they suggested using a variety of measures to assess participants, especially individuals with HL.

Procedures and Validity

Procedures and validity are first discussed for the questionnaire study and then for both of the experimental studies since several measures are included in the simulator study and the field study.

Questionnaire Study

Along with questions about hearing and transport habits, aspects found in the literature to be avoided by older drivers were included in the questionnaire (long distances, rush hours, darkness, poor weather, road surface conditions, and driving in unfamiliar areas) (D'Ambrosio, 2008; Gwyther, 2012; Hakamies-Blomqvist, 1994; Rothe, 1990). In the questions about traffic incidents and accidents definitions from a report from the Swedish Road Administration (STRADA, 2007) were used.

Questionnaire responses were mainly scored using a 5-point scale. The odd number was chosen to allow neutral answers, and 5 points was chosen instead of a larger number because the data were not expected to be skewed in either direction (Johnston, 2008). The alternatives of “*do not know*” or “*not relevant*” were also included to avoid forcing participants to tick wrong alternatives. A few open questions were also included to allow respondents to answer in their own words, and likewise after each closed question there was room for comments.

Experimental Studies

According to de Waard (1996), self-report scales and performance measures are the most appropriate for workload assessment, and a useful experimental design in traffic research is to compare task performance in an experimental (e.g., mental load) condition with performance under baseline conditions. Evaluation of workload due to complexity should, according to de Waard et al., either involve an increase in road complexity or an increase in task complexity, for example with the addition of a secondary task. This approach was used in both experimental studies. In the simulator study, load conditions with and without a secondary task were compared with baseline conditions with and without the secondary task. In the field study, road complexity varied between city and ring road, while task complexity either by varied including a tactile support in the navigation system or leaving that out. Self-report scales during (only in the simulator study) and after the drive were used, as well as performance measures.

Critical incidents, law violations, and LP errors are measures of driving performance and have been used as such in task-performance assessments (e.g., Pohlmann & Traenkle, 1994). In particular, complex behavior, such as the occurrence of critical incidents or behavior in a complex driving environment, can be easier, or more accurately, detected and judged by an observer than captured in a single performance measure (de Waard, 1996).

Pretests

In both experimental studies, hearing tests were performed on all drivers with NH and for participants with HL audiograms were provided from the audiology clinic. The inclusion criterion for the NH group was a hearing threshold of maximum 20 dB at each frequency (500, 1000, 2000, and 4000 Hz), measured with a pure tone audiometer. Inclusion criterion for the HL group was a moderate HL (41-60 dB) according to WHO categories (Arlinger, 2007), measured with a pure-tone average of 4 mean values, PTA4 (means of 500, 1000, 2000, and 4000 Hz).

In the field study (Paper IV), more pretests were included to control for differences between the experimental groups. Apart from HL, normal consequences of aging also include declining visual abilities, such as visual acuity and contrast sensitivity (e.g., Risacher et al., 2013; Heyl & Wahl, 2012) and cognition (e.g., McDowd & Shaw, 2000; Verhaeghen et al., 2003; Mayr et al., 2001; Verhaeghen et al., 2005, Craik & Salthouse, 2000; Phillips & Lesperance, 2003). Relationships between sensory and cognitive losses in older adults have also been presented (Clay et al., 2009; Heyl & Wahl, 2012; Holland, 2009; Vreeken et al., 2013). Therefore, in the field study, vision tests and cognitive tests were included to control for differences between the groups.

Clinical vision measures included binocular *distance visual acuity* using a logMAR chart (Ferris, Kasso, Bresnick, & Bailey, 1982) and binocular *contrast sensitivity* (log CS) using the Pelli-Robson chart (Pelli, Robson, & Wilkins, 1988). Cognitive tests included: *verbal ability* (The F-test, Psykologiförlaget, Stockholm); a cognitive test battery, including *physical matching*, *physical lexical matching*, *rhyme* and *reading span* (Hällgren, Larsby, Lyxell, & Arlinger, 2001); a computerized dynamic TMT, shown to be related to driving performance (Lehtonen, Dahlström, Hiltunen, & Summala, 2012), and the Useful Field of View test (UFOV), measuring skills thought to be used during driving (Ball & Owsley, 1993).

Secondary Task

In the simulator study, to create 2 levels of cognitive workload in the secondary task the phonological similarity effect was used (Conrad & Hull, 1964; Baddeley, 1968; Hitch & Halliday, 1983), and the sequences consisted of randomized letters that were either phonologically alike (e.g., BDPT) or not phonological alike (e.g., RKNJ). Each letter was displayed for 0.7 seconds, which is an adaptation of Sternberg's scanning paradigm (Sternberg, 1966). The display time had to be long enough for recognition of the letters, but short enough for the participants to keep their eyes on the display.

Performance Indicators

Performance indicators in the simulator study were mean LP, SDLP, minimum TLC (TLCmin; Brookhuis, Waard, & Fairclough, 2003), mean driving speed, SD driving speed, and secondary task performance. For subjective ratings during the simulator test drive, the following question was presented on the screen after each event: How critical did you experience the situation to be? The participants answered on a scale from 1 = not critical at all to 7 = extremely critical. This is an adaptation (specifically the dimension of the degree of complication) from the Situation Awareness Rating Technique (SART) 10 Dimension-scale, with each dimension ranging from 1-7 (Endsley & Garland, 2000).

In the field study, mean driving speed and SD driving speed were included along with eye tracking (specifically frequency and length of fixations) and driving performance assessment according to an on-road protocol (Selander, Lee, Johansson, & Falkmer, 2011).

Table 1. Participants' demographic details and data collection method in the studies

Study	Participants	Gender (Male/Female)	Age Mean (SD) Male/Female	Data collection method
I	93 self-reported NH 48 mild HL 105 moderate HL 47 severe HL 18 profound HL	50/43 17/31 44/61 28/19 7/11	71.5 (13.2)/63.4 (14.5) 69.0 (11.1)/68.7 (12.4) 74.8 (7.7)/61.1 (15.9) 55.5 (15.1)/75.1 (14.7) 57.3 (12.6)/65.8 (9.7)	Questionnaire survey
II	24 NH 24 moderate HL	12/12 13/11	60.1 (7.1)/59.6 (5.0) 62.0 (7.9)/61.0 (9.8)	Driving simulator study with driving performance, eye tracking, and survey
III	16 NH 16 moderate HL	5/10 7/8	51.2 (8.3)/52.8 (11.0) 60.2 (12.4)/53.0 (13.3)	Field study with eye tracking, questionnaire and driving assessment

Participants and Data Collection

For the questionnaire survey, participants were recruited from the local branch of the Swedish hard of hearing association. A control group with normal hearing (NH), matched with age, gender and geographical location, was then selected from a commercial database. The survey was also used to recruit participants for the other studies by including a question about their interest in taking part in further research in the field of HL and traffic safety. The VTI participant database was used to recruit participants with NH. Information about participants' demographic details is listed in Table 1 together with the data collection method used for each study.

Design and Statistical Analyses

Questionnaire Survey

Logistic regression (binary for dichotomous questions answered by “yes” or “no” and ordinal for questions with more than 2 ordered alternatives) was used to analyze the results of the questionnaire study because it was explorative and had no inbuilt expectations to examine. This is a type of regression analysis with binary or ordinal response variables. The probabilities describing the possible outcomes of a single trial are modelled as a function of the explanatory (predictor) variables, using a logistic function (Bishop, 2006).

All predictor variables were entered simultaneously, since there was no presumption of which one would explain more. The results from the logistic regression are presented using odds ratio (*OR*), which quantifies how strongly the presence or absence of property A in the response variable is associated with the values on the predictor variables (McHugh, 2009; Mosteller, 1968). That is, this gives a measure of the influence of the predicting variables (e.g., degree of HL, gender, age) on the dependent variable (e.g., having a driver's license). $OR = 1$ means no influence, $OR > 1$ means an increasing probability, and $OR < 1$ means a decreasing probability.

Driving Simulator Study

The driving simulator study had a $2 \times 2 \times 2$ factor design with the fixed factors *hearing status* (NH vs. HL), *gender* (men vs. women), and *difficulty level* (lower vs. higher). Participant (participants 1-48) within *hearing status* and *gender* was included as a random factor. On driving behavior measures (e.g., speed) and secondary task, analysis with planned comparisons within and between the Hearing status levels was carried out using a mixed model. For the post-trip questionnaire, with questions on subjects including subjective driving performance on ordinal scales, logistic regression and *OR* were used.

Analysis of gaze data was conducted in 2 steps. The strategy for analyzing the distribution of glances was to start with a model as comprehensive as possible, with several variables, interactions, and multidimensional responses. A multivariate analysis of variance (MANOVA) was performed to examine whether *condition* (with or without secondary task), *hearing status*, *gender* or any two-factor interactions of these had an effect on the distribution of glances, where the distribution is governed by a vector representing the 7 target gaze zones. In this model, hearing, gender and condition were included as fixed variables, and a participant nested within hearing and gender was included as a random variable. The significant interaction effect of condition and hearing led to the analysis of each condition and each hearing status. ANOVA (analysis of variance) were performed to test hypotheses examining one zone at a time.

Field Study

In the field study a $2 \times 2 \times 2$ factorial design with the between-groups factor *hearing status* (NH vs. HL), and the two within-groups factors *system information* (visual vs. visual tactile), and *complexity* (lower vs. higher) were used. Generalized estimating equations (GEEs) were used to model correlated data from this repeated measures design. GEEs are used to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes, and have the advantage of overcoming the classical assumptions of statistics, for example independence and normality, which are too restrictive for many problems (Liang & Zeger, 1986; James & Joseph, 2003).

GEEs were used on the following linear or continuous outcome measures: speed, on-road performance, gaze behavior patterns, and usability questions. Predictor variables were *system information* (within subjects), *hearing category*, and *age* (between subjects). Outputs were Wald statistics (χ^2), showing the significance, and an unstandardized regression coefficient (*B*), presenting the relationship between the groups. For background questions in the questionnaire, cognitive tests, and vision tests one-way ANOVAs were performed.

SUMMARY OF STUDIES AND PAPERS

In experimental psychology there are often several parts of a study presented in one paper. In this thesis, the studies are fewer and larger and have generated one or 2 papers each, which is more common in traffic safety research.

An overview of studies, papers, and findings is presented in Figure 3. Three studies were conducted and generated four scientific papers, which are included in this thesis. Since the initial level of knowledge was low and somewhat contradictory, a questionnaire study was the first step on the path to evaluate differences in traffic safety and mobility related to HL. The results from the first study are presented in the first scientific paper and also included in the background to the second study conducted in the driving simulator. The results from this study generated the second and third scientific papers and were (together with the results from the questionnaire study) included in the background to the third study conducted in real traffic. This study generated the fourth scientific paper. Summaries of each study are presented in the following sections.

Study 1: A Questionnaire Survey

Paper I: The Influence of Hearing Loss on Transport Safety and Mobility

Purpose

The purpose of study 1 was to examine how road users with different degrees of HL, compared to road users with NH, experience traffic safety and mobility. Specifically, three general research questions were investigated: how HL affects the choice of transportation type (e.g., driving your own car vs. public transport); personal view of HL in relation to transport situations, and the need for and design of driver support systems (e.g., collision warning, parking aid, navigation systems, lane keeping systems) for drivers with HL.

Method

A questionnaire survey was conducted with participants recruited from the local branch of the Swedish Association for Hard of Hearing People (HRF). A NH control group, random and matched by age, gender and geographical location, was selected from a commercial database. From audiogram data, participants were sorted into groups according to their degree of HL. A web-based questionnaire was constructed to capture the 3 research questions mentioned above. With assistance from HRF, letters were sent out to members of their local branches with an invitation to take part in the study. There was also the possibility of receiving a paper version of the questionnaire. The response rate was 35% (n = 194) in the group with HL and 42% (n = 125) in the group with NH. The individuals with hearing loss were grouped into four groups according to the degree of their hearing loss (mild, moderate, severe, and profound). After receiving permission from the participants, audiograms were provided by the local audiology clinic for the HL group.

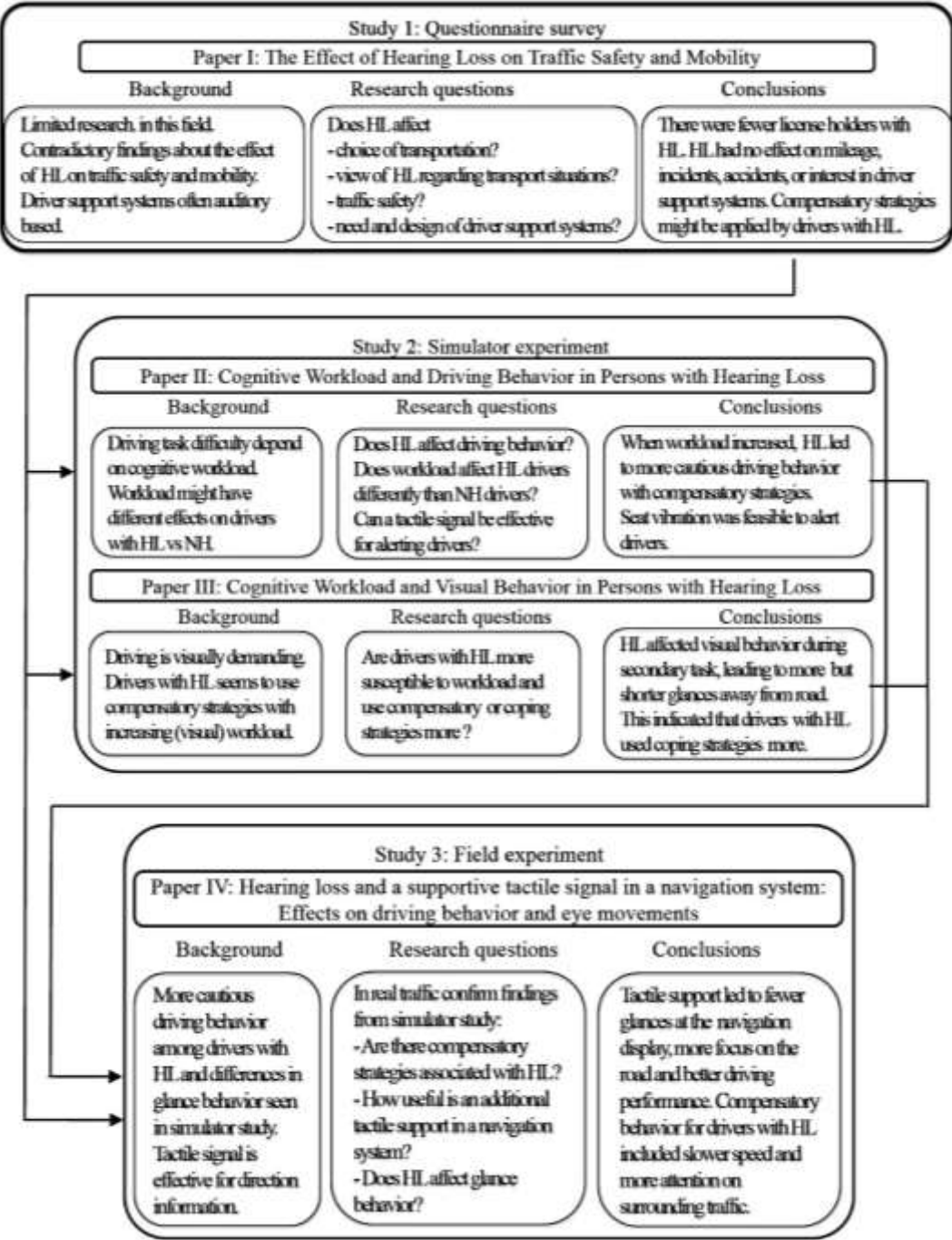


Figure 3. Overview of studies, papers and findings.

Results

A higher degree of HL was associated with less likelihood of having a driver’s license. However, individuals with HL who had a driver’s license, drove as much as NH drivers. HL was related to the criteria for choosing the type of transport, such that individuals with more

HL rated written information as more important and time cost and safety as less important than those with less HL. However, in the aggregate, no difference between the groups could be shown in the distribution of how much each mode of transportation was used.

With a few exceptions, HL did not affect the ratings of importance of hearing for different transportation types. The exceptions were walking and public transportation, where respondents with moderate HL rated hearing as significantly more important than those with NH. There was no effect of HL on involvement in incidents or accidents.

Degree of HL was related to several questions of driving ability, and the general pattern was that individuals with a higher degree of HL rated driving ability less affected by HL. This indicates that they might be using compensatory strategies. The interest in a warning system for inattention and the attitude toward strengthening of or complementing auditory information in traffic situations was high regardless of HL.

Conclusion

From this study, it was concluded that HL influences the prevalence of a driver's license and criteria for choosing type of transportation; however, HL has no effect on the distribution of how much each type of transportation was used. In general, respondents with more HL were less concerned about the effect of HL, indicating that they might be using compensatory strategies (adjustments to compensate for a decline). The interest in a warning system for inattention and the attitude toward strengthening of auditory information in traffic situations was high regardless of HL or not. This suggests a need for further research on compensatory strategies and on the design of support systems accessible for drivers with HL.

Study 2: A Driving Simulator Study

Purpose

A simulator study was conducted to compare the effect of cognitive workload in individuals with and without HL, respectively, in driving situations with varying degree of complexity. The effectiveness of a tactile signal used to call for driver attention was also evaluated.

Method

Twenty-four participants with moderate HL and 24 with NH experienced 3 different driving conditions: baseline driving on a 35-km long rural road with a speed limit of 70 km/hr; critical events with a need to act fast; and a parked car event with the possibility to adapt the workload to the situation (e.g., by deciding whether or not to focus on the secondary task). A secondary task (observation and recalling of 4 visually displayed letters) was present during the drive, with 2 levels of difficulty in terms of load on the phonological loop.

A tactile signal, presented by means of a vibration in the seat, was used to announce the secondary task and thereby simultaneously evaluated in terms of effectiveness when calling for driver attention. The letters were displayed on a screen at a low down angle, so that the driver had to look away from the road. Twice per minute, drivers were prompted by the tactile signal in the seat to first look at and then read back a complete sequence of 4 letters appearing

on the display. The total duration of the task corresponds to a critical situation in which drivers take their eyes off the road to look at the display.

For the critical events, to create near collisions, the drivers were distracted by means of the secondary task, and then “pushed” across the median toward an oncoming vehicle by introducing a steering angle in the simulated vehicle without submitting this information to the motion platform. The parked car event was a situation when the participants saw a parked car ahead (from 360 meters) with warning lights activated. This study generated 2 papers with different focus presented separately below.

Paper II: Cognitive Workload and Driving Behavior in Persons with Hearing Loss

In this paper, objective driver behavior measures from the simulator study accompanied by subjective ratings during and after the test drive are presented, as well as the result from secondary task and the questionnaire after driving.

Method

Driver behavior measures were mean driving speed; SD of Driving speed; mean LP; SD of LP; and minimum time to line crossing. The secondary task was analyzed with respect to the number of correct recalled letters per task, number of skipped letters per task, and number of correct recalled letters per task ignoring the order. Subjective ratings during and after the test drive were included to evaluate the realism of the simulated event. There was also a questionnaire after driving including self-reported driving behavior, realism of the simulator, and evaluation of the tactile signal used to announce the secondary task.

Results

HL had no effect on driving behavior during baseline driving, where no events occurred. During both the secondary task and the parked car event, HL was associated with decreased mean driving speed compared with baseline driving. Participants with HL drove approximately 6 km/hr slower during the secondary task than NH participants did (approx. 65 km/hr vs. 70 km/hr), $F(1, 44) = 7.68$, $p = 0.01$, $\eta^2 = 0.14$. At the parked car event, participants with HL drove approximately 5 km/hr slower, $F(1, 44) = 2.42$, $p = 0.05$, $\eta^2 = 0.05$.

The effect of HL on the secondary task performance, both at baseline driving and at critical events, was more skipped letters and fewer correctly recalled letters. Furthermore, at critical events task difficulty affected participants with HL more. There was no effect of HL on the secondary task at the parked car event. Participants were generally positive about the use of a tactile signal in the seat as a means for announcing the secondary task. There was no effect of HL on self-reported driving performance.

Conclusion

It was concluded that differences in driving behavior and secondary task performance related to HL appear when demands increase, either when driving demands exceed baseline driving or when the secondary task becomes more cognitively demanding or both. Increased demands lead to a more cautious driving behavior with a decreased mean driving speed and less focus on the secondary task. This indicate that HL is associated with both compensatory

strategies and coping strategies. Seat vibration was found to be a feasible way to alert drivers with or without HL.

Paper III: Cognitive Workload and Visual Behavior in Elderly Drivers with Hearing Loss

The objective of this paper was to compare visual behavior in individuals with NH and with moderate HL, and reveal possible differences by analyzing eye-tracking data from the simulator study.

Method

The cockpit was divided into 7 target zones: windshield, right, left, center mirror, speedometer, task display, other. Gaze data were analyzed with respect to distribution of glances, fixations in target zones and eye movement behavior. Eye gaze behavior was assessed during normal driving and driving with the loading secondary task. The following performance indicators were used: number of glances away from the road, mean duration of glances away from the road, maximum duration of glances away from the road, and the percentage of time when the driver was looking at the road. During the secondary task, additional eye movement data were assessed in terms of number of glances to the secondary task display, mean duration of glances to the secondary task display, and maximum duration of glances to the secondary task display.

Results

Vertical and horizontal gaze directions showed only small differences between the NH and HL groups, such that the HL group tended to have narrower and more distinct gaze manners corresponding to the speedometer and the mirrors in the cockpit. There were also some indications that, during the secondary task, the HL group looked in the center rear-view mirror and further to the right more often than the NH group. Also, it could be seen that glances toward the secondary task display were preceded by glances to the mirrors more often in the HL group than in the NH group.

The main result from the analysis of target zones (the objects that the driver looks at within the car's cockpit) was that during the secondary task, drivers with HL looked twice as often in the rear-view mirror as they did during normal driving and twice as often as drivers with NH regardless of the driving condition.

Also, during secondary task, drivers with HL showed a different strategy when looking away from road. They looked away from the road as much as drivers with NH; however, with more frequent glances of shorter duration.

Conclusion

It was concluded that differences in visual search behavior between drivers with NH and drivers with HL are bound to driving condition. During the secondary loading task, drivers with HL looked twice as often in the rear-view mirror than during normal driving and than drivers with NH, regardless of driving condition. Moreover, during secondary task, drivers with HL looked away from the road as much as drivers with NH, but with more frequent glances of shorter duration. The results also indicate that drivers with HL performed a visual scan of the surrounding traffic environment before looking away toward the secondary task

display. This more active visual search behavior might indicate that drivers with HL use compensatory strategies to a higher extent than NH drivers.

Study 3: A Field Study in Real Traffic

Paper IV: Hearing Loss and a Supportive Tactile Signal in a Navigation System: Effects on Driving Behavior and Eye Movements

Purpose

The purpose of the third study, conducted in real traffic, was to replicate and further examine findings from previous simulator study, namely driver compensatory strategies associated with HL and evaluate possible effects of additional tactile support in a navigation system. Furthermore, since the simulator study indicated differences in gaze behavior between drivers with and without HL, eye-tracking data was analyzed as part of the study

Method

Thirty-two participants (16 HL and 16 NH) performed two pre-programmed navigation tasks in an urban environment. In one task, participants received only visual navigation information, while in the other vibration in the seat was used as a complement. This tactile support was given in the left or the right side of the driver's seat to indicate the direction of the next turn. Performance indicators and measures included driving speed, driving behavior observations (using a protocol filled out by a test leader), eye tracking, and a post-drive questionnaire. SMI glasses were used for eye tracking, recording the point of gaze within the scene. Analysis of gaze data was performed on predefined regions such as windscreen, mirrors, navigation display, and speedometer. The questionnaire examined participants' experience of the two navigation tasks in terms of their feelings of safety, usefulness, and comfort.

Results

On road sections with a speed limit of 70 km/hr, participants with a HL drove 4 km/hr slower than participants with NH. The same tendency was also seen on sections with a speed limit of 50 km/hr; however, this result was not statistically significant.

During observed driving, participants with NH had on average 0.3 more marks on the measure 'speed too high' than participants with HL, and participants with HL had 0.5 more marks on the measure 'speed too low' than those with NH. Participants with HL also averaged 1 mark higher on the measure 'uneven speed' than participants with NH. Participants with HL spent on average 1.4% more time looking in the rear-view mirror than NH participants. HL participants looked an average of 3 times as often (0.3 times per minute vs. 0.1 times) in the rear-view mirror as the NH group, but there was no effect on the duration of glances.

When driving without the tactile information activated, participants had on average 0.5 more marks on the measure 'inattention straight' and 0.5 more marks on the measure 'position distance' than when they had the tactile information. With the tactile information activated, participants looked on average 7% less at the navigation display and consequently

on average 7% more through the windscreen than without the tactile information. The number of glances per minute revealed that without the tactile information, on average participants looked once more per minute at the navigation display and there was no effect on the duration of glances. With the tactile information activated, both hearing groups were significantly more satisfied with their ability to navigate and with the help they got from the system. Participants also felt safer and more comfortable in this condition. Furthermore, participants in the HL group were significantly more satisfied than the NH group with their ability to navigate when the tactile information was activated. There was no effect of HL on self-rated driving performance.

Conclusion

Results from this study revealed that drivers with HL drove more slowly than drivers with NH, drove slower and looked more often in their rear-view mirror. These compensatory strategies suggest a more cautious driving behavior. The study also showed that tactile support leads to higher satisfaction with the navigation system, less time spent looking at the navigation display (in terms of frequency), and thus more focus on the road and better driving performance (in terms of both attention and distance).

GENERAL DISCUSSION

The general aim of this thesis was to investigate traffic safety and mobility for older individuals with HL from the perspective of cognitive psychology. With the limited previous research and relatively low level of knowledge in this field the approach has been exploratory with subjective and objective performance indicators, and the findings from each study have been included for further evaluation.

The questionnaire survey investigated how HL affects the choice of transportation, personal views of HL in relation to transport situations, and the design requirements for driver support systems accessible for road users with HL. The simulator study examined differences in driving behavior and visual behavior between drivers with NH and drivers with HL and the effectiveness of a tactile signal to alert drivers. The field study further examined possible compensatory strategies associated with HL, the usefulness of an additional tactile support in a navigation system, and differences in eye movement patterns.

Summary of Results

Summarizing and abstracting the effects of HL throughout the studies included in this thesis reveal that the effects of HL on traffic safety and mobility are existing, but small (in terms of effect sizes), often bound to workload condition and rather specific, but still consistent in the replicated studies.

The questionnaire revealed that differences in transportation habits related to HL include the less likelihood of having a driver's license and a higher valuing of written information, with the latter possibly prioritized before time and safety issues. Moreover, respondents with more HL were less concerned about the effect of HL, indicating that they might be using

compensatory strategies. In addition, the interest in a warning system and the attitude toward strengthening of or complementing auditory information in traffic situations was high regardless of hearing ability. These are all new findings, pointing to a few potentially important effects of HL from a traffic safety and mobility perspective.

Furthermore, the questionnaire revealed that HL was not related to the frequency of using any of the transportation types (e.g., cars, cycling, or public transportation). There was no difference in the patterns with regard to transportation types during wintertime or any effect of HL on self-reported incidents or accidents.

In the experimental studies, differences related to HL in terms of driving behavior (mostly lower driving speed) were bound to driving conditions and occurred when the complexity of driving task increased (simulator study) or at a higher speed limit (field study). There was also an effect of HL on visual behavior, indicated in the simulator study and confirmed in the field study. Drivers with HL had a more active visual behavior with more frequent glances on the secondary task (simulator study), more frequent glances in the rear-view mirror, and more general scanning of the environment before looking away from the road (simulator study). Secondary task performance was lower for the HL group, with more skipped letters, suggesting this group is less willing to perform this task. These are all new findings, in line with the expectations, and the effect of HL on driving behavior and on visual search behavior suggest people with HL use more compensatory strategies and coping strategies leading to a more cautious driving behavior.

The tactile signal in the driver seat was found useful in both experimental studies, both for driver attention and for facilitating navigation with a GPS navigation device. The field study showed that the tactile support led to higher satisfaction with the navigation system. The tactile support also led to less time spent looking at the navigation display, and thus more focus on the road and better driving performance in terms of both attention and distance. These are new findings, supporting the expectations and adding to the growing body of evidence of the benefits of using tactile information in cars (van Erp & van Veen, 2004; Ho, Tan, & Spence, 2005; Ho, Reed, & Spence, 2006).

In the simulator study (study II), HL had no effect on driving behavior at baseline driving, where no events occurred and when no secondary task was present. In the field study, the effect of HL on driving speed displayed the same pattern, however was not significantly lower, at the lower speed limit. In neither of the experimental studies, there was an effect of HL on the self-rated driving performance.

Choice of Transportation

ICF, conceptualizing functioning and disability as an interaction between an individual's health condition, contextual factors of the environment and personal factors, includes mobility in activity and participation (WHO, 2001). There were some effects of HL found, which according to the hierarchical model suggested by Michon (1985), belong to the top level, where strategic decisions are made by control processing such as the choice of type of transport.

That the likelihood of having a driver's license is negatively associated with the degree of HL is a new finding. There was no effect of HL on mileage and also no relation between the degree of HL and driving cessation. This suggests that in the studied population difficulties or

lack of interest associated with HL and car driving emerge when deciding whether or not to learn to drive. This is an indication of individuals with HL using coping. Knowing that difficulty in taking part in activities increase with the degree of HL (Gopinath, Schneider, Hickson, et al., 2012a; Grue et al., 2009; Wallhagen et al., 2001; Schneider et al., 2010), one could speculate that taking driving lessons might be too difficult for some individuals with HL, as some respondents mentioned. The main focus in this thesis is on those with moderate HL who are still driving; however, this driver's license issue is something for further research, since car access can act as a compensational tool for functional limitations (Sirén & Hakamies-Blomqvist, 2004, 2009) and is associated with better health and well-being among the elderly (Ellaway, Macintyre, Hiscock, & Kearns, 2003; Macintyre, Hiscock, Kearns, & Ellaway).

That individuals with HL sometimes find written information more important than time cost, and safety issues is also a new finding. According to Rumar (1988), there is always a risk in being mobile, and risk can be divided into statistical and experienced risk. There is a possibility that individuals with HL feel safer when they have written information and therefore prioritize this before statistical safety and time cost. Furthermore, individuals with moderate HL expressed a higher need to be able to hear on public transportation than those with NH. This is in line with Gopinath et al. (2012), who found that using public transportation is harder for individuals with HL, and there might be a need for more written information on public transportation to increase experienced safety, activity and participation for individuals with HL.

Driving Behavior

Motivational driving behavior models all have in common maintenance of the acceptable level of risk (Wilde, 1982; Fuller & Santos, 2002; Fuller, 2005, 2007; Fuller et al., 2008; Fuller, McHugh et al., 2008; Vaa et al., 2000; Vaa, 2003, 2007, 2011; Näätänen & Summala, 1974). Consistent with results from Wu et al. (2014), effects on driving behavior for individuals with HL emerge when driving task exceeds baseline driving. The main effects from the simulator study are consistent with Fuller (2005), suggesting that manipulating driving speed and engagement in a secondary tasks are the primary mechanisms for maintaining the preferred level of difficulty.

Lewis-Evans (2012) concluded that speed is not only a conscious choice but rather a challenge to be handled, at least on some level, by automatic processes, and that the existence of these processes can be inferred when the cognitive capability of drivers is loaded. There is a higher risk of cognitive fatigue in individuals with HL, and also possibly a different perception of speed (cf. Evans, 1970; Ohta & Komatsu, 1991). Taking this together, there is a possibility that drivers with HL may have decreased speed control, and therefore drive slower and at a more uneven speed (field study).

In addition, considering Lewis-Evans' (2012) suggestion that there is a threshold to account for the perception of subjective variables (e.g., task difficulty, effort, comfort, crash risk, and feeling of risk), drivers with HL might experience an increased feeling of risk (Rumar, 1988) and therefore aim to maintain a different level of risk. This increased feeling of risk might come from a decreased perception of the surroundings and decreased feedback leading to a decreased feeling of control, which is also reflected in the gaze behavior. That is,

they might compensate for the increased risk by driving at a lower speed (e.g., Haustein et al., 2013), and be less engaged in distracting activities, which is a coping strategy (e.g., Ben-Zur, 2009; Fofanova & Vollrath, 2012).

Visual Behavior

Drivers with HL showed more watchful manners with regard to visual behavior. The higher frequency of glances in the mirrors point to the fact that individuals with HL might value this kind of information more than that with NH. This new finding is in line with the expectations of a compensatory strategy with a more active visual search behavior, due to the fact that hearing gives us valuable spatial and temporal resolution. This is also in line with Wilson and Eggemeier (1991), who found a relationship between frequency of fixation and instrument importance, and this, might be a part of a compensatory behavior.

Visual search strategy is according to traffic inspectors the most important concept related to risk awareness (Lidestam et al., 2010). The difference between drivers with HL and drivers with NH in the strategy of looking away from the road was apparent during the secondary task in the driving simulator. Drivers with HL looked away more often and for a shorter period each time; however, there was no effect of HL on total time with the eyes off the road. Again, this behavior might be connected to the experienced safety and feeling of risk, suggesting that avoiding long glances away is a coping strategy on the part of those with HL.

With the descriptive and explorative approach of this thesis, the relationship between the secondary task performance in Paper II and the gaze behavior in Paper III is interesting. In Paper II, we concluded that drivers with HL might be less willing to make an effort to perform the secondary task. Their lower performance might also be due to the fact that the task loads on the phonological loop and is thus more cognitively demanding for drivers with HL. An acquired HL may lead to a deteriorated function in the phonological loop, which means that drivers with HL should need to look at the letters for a longer time. However, as seen in Paper III, on the contrary they look at the secondary task display more frequently and with shorter duration compared to drivers with NH. This indicates that with the limited capacity during the secondary task, which also results in decreased speed for drivers with HL, driving safety is prioritized before performance on the task, which could be a sign of compensatory behavior.

Driver Assistance Systems

In the questionnaire survey, the interest in driver assistance systems was not affected by HL and suggested evaluation of alternative modality for driver support systems. From the classifications suggested by Carsten and Nilsson (2001), the HMI aspect (operating and communicating with the system) and the traffic safety aspect (system influence on driving behavior, including changes in interactions with other road users) are relevant for evaluating the effect of HL. Concerning the HMI aspect, and in line with the expectations and previous findings (e.g., van Erp & van Veen, 2004;), the tactile signal in the driver's seat was useful in both experimental studies, for both calling for driver attention and facilitating navigation with

a GPS device. Furthermore, of high relevance for the traffic safety aspect, regardless of hearing status, the tactile support led to higher satisfaction with the navigation system, less time spent looking at the navigation display, more focus on the road, and better driving performance. This was in line with the expectations too, and may increase traffic safety for drivers regardless of HL or not, since this may release other heavily loaded sensory channels (c.f. Wickens and Hollands, 1999) and therefore potentially provide a major safety enhancement.

Methodological Discussion

The advantages of performing a simulator study also come with limitations (Mullen, Charlton, Devlin, & Bédard, 2001; Nilsson, 1993). For example, motion, velocity and acceleration ranges are limited, it is impossible to fully represent a real traffic environment, and participants may suffer from simulator sickness, a type of motion sickness experienced only in simulators (Nilsson, 1993).

There was an effect of HL, such that drivers with NH experienced the simulator as more realistic. Also, some effects of eye movement behavior indicated in the simulator were confirmed in the field study. These two effects might be related, such that the realism was needed for some of the effects to show. Also, female drivers with HL reported the highest values of simulator sickness, which might be connected to the realism of the simulator, such that higher experienced realism lead to less simulator sickness.

Age-related HL is the most common type of HL and thus it is most relevant to look at the effects of HL in the group of older people. With a quasi-experimental design (HL vs. NH) follows a heterogeneity between groups. To create as homogenous groups as possible, apart from hearing status, the aim was to recruit participants under 65 years of age to avoid age effects.

CONCLUSION

From the studies included in this thesis, it can be concluded that there are effects of HL on both traffic safety and mobility, such that individuals with HL are less likely to have a driver's license, more likely to show a more cautious driving behavior, and will sometimes prioritize experienced safety before statistical safety. The effects of HL revealed in this thesis are new findings and add to the knowledge and understanding of the influence of HL on traffic safety and mobility. Differences found consistently point to a generally more cautious behavior, which suggests an effect of HL on experienced safety.

Compensatory strategies and coping strategies associated with HL are bound to driving complexity and appear when complexity increases. These strategies include driving at lower speeds, using a more comprehensive visual search behavior (compensatory) and being less engaged in distracting activities (coping).

The influence of HL on the choice to drive a car is limited to the decision of whether or not to learn to drive, since HL does not affect mileage or driving cessation.

Evaluation of a tactile signal suggests that by adding a tactile modality, some driver assistance systems can also be made accessible to drivers with HL. At the same time, the systems might be more effective for all users, since visual resources can be more focused on the road, which could generally increase both traffic safety and mobility.

Based on the results in this thesis, drivers with HL cannot be considered an increased traffic safety risk, and there should be no need for adjustments of the requirements of hearing for a license to drive a car.

SUGGESTIONS FOR FUTURE RESEARCH

This thesis presents exploratory and experimental research on the effects of HL on traffic safety and mobility. Some effects of HL have been found (suggesting a more cautious driving behavior), which can be used in future recommendations. There are also some aspects worth looking into further. Generally, it is possible that individuals with disabilities (of different kinds) might contribute to a better understanding of how to design better driver support systems. Since they are more sensitive to higher workload, they might be able to indicate how to develop support systems, which might be more useful for all drivers.

The compensatory strategies found, indicating maintenance of a different level of difficulty, suggest further investigation of the effect of HL on feeling of risk.

The possibility of individuals with HL experiencing higher safety when there is written information and therefore prioritizing this before statistical safety and time cost is worth further evaluation.

The accessibility of written information on public transportation is relevant to evaluate, since differences appeared in this and other studies (Gopinath et al., 2012b) related to the degree of HL.

Less likelihood of having a driver's license suggests further evaluation of the driving lesson situation for individuals with HL.

Positive effects of tactile signals in driver assistance systems suggest further research on how to implement accessible signals in these systems.

The effect of the use of hearing aid technologies when driving should be further investigated. This was not included in the studies presented in this thesis although there is reason to believe that the right aid can increase traffic safety and mobility (e.g., McCloskey, Koepsell, Wolf, & Buchner, 1994; Wu et al., 2014).

The fact that there is a decline in various abilities (e.g., cognitive, visual, auditory) associated with normal aging, makes further examination of the effects of decline in each type and combination of types, and also the effects of aid for each type, relevant for future study.

The effects of HL on perception and decision-making have not been examined explicitly in studies presented in this thesis. However, the results pointing at a difference in experienced safety associated with HL suggest that these aspects should be further studied.

The studies included in this thesis focus on age-related HL. It would be of interest to look at the effects of other types of HL such as genetic deafness or individuals with CI.

It would be relevant to study the effects of HL on cognitive fatigue and of cognitive fatigue on traffic safety, since cognitive fatigue is a known effect of HL (e.g., Moradi et al.,

2014; Rönnberg et al., 2013) and could lead to decreased attention. Also, studying the effect of reducing cognitive fatigue on traffic safety can add to the understanding of the problem.

In this field of research, investigation into specific effects of decline in different aspects of EF, rather than attention to the broad perspective, is more likely to yield a more comprehensive picture.

It could be worthwhile to study other modalities of driver assistance systems than auditory and tactile, such as ambient (light), and to evaluate which modalities and ways of presenting the information are most suitable to which driver group or in which situations.

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Chapter 31

GENETICS OF HEARING LOSS: TESTING METHODOLOGIES AND COUNSELING OF AUDIOLOGY PATIENTS AND THEIR FAMILIES

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ABSTRACT

Approximately 2 to 3 per 1,000 newborns are diagnosed with permanent hearing loss. It is estimated that 75 to 80% of these cases are due to a genetic etiology. Genetic hearing loss can be syndromic, meaning other clinical features are present along with the hearing loss; or nonsyndromic, meaning hearing loss occurs in isolation. More than 400 genes have been reported to contribute to hearing loss and more than 100 genes have been reported to cause nonsyndromic hearing loss. Genes causing hearing loss display various modes of inheritance, with autosomal recessive being the most common. With so many cases of hearing loss having a genetic etiology, audiologists are certain to encounter these patients on a fairly regular basis. Audiologists who possess basic knowledge about genetics are better equipped to recognize when a genetics referral is warranted, thereby enhancing patient care. A genetics evaluation can yield valuable information for patients and their families, such as prognosis, estimates of recurrence risks, and diagnosis of other family members. A variety of testing methodologies are available, and are chosen based on such considerations as clinical presentation, cost, analysis time, laboratory availability, previous testing performed, and likelihood of a positive result, among others. As technologies for genetic testing advance, sequencing techniques such as whole exome sequencing, genomic sequencing, and targeted sequencing are becoming more affordable, allowing for more patients to receive a diagnosis than was previously possible.

Keywords: genetics, hearing loss, deafness, audiology, hearing loss counseling, sequencing, syndromic hearing loss, nonsyndromic hearing loss, genetic testing

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1. INTRODUCTION

Approximately 2 to 3 per 1,000 newborns will be diagnosed with permanent hearing loss [1], making it one of the most common birth conditions. When factoring in delayed-onset and minimal hearing losses, prevalence increases to 20% in adolescence [2]. Historically, 50% of these cases have been attributed to genetic causes and 50% to environmental causes [3, 4]. However, estimates in recent years have suggested that the true proportion of permanent childhood hearing loss cases attributable to genetics in developed countries is closer to 80% [5]. This perceived increase in genetic hearing loss is likely due to a decrease in cases caused by infections, such as rubella. Prenatal rubella infection, a common cause of deafness in the 1960s and prior, has largely been eradicated in developed countries through vaccination [6]. Thus, the proportion of permanent hearing loss cases with a genetic etiology has increased. In addition, it is unknown how many genetic causes are undiagnosed. New epidemiological studies are needed to more accurately characterize the etiology of permanent childhood hearing loss.

The human genome contains approximately 20,000 genes [7]. These genes code for proteins which carry out all of the functions necessary for life. More than 400 genes have been reported to contribute to hearing loss [8] and more than 100 genes have been reported to cause hearing loss in isolation [9]. For a better understanding of genes, it is important to discuss what makes up genes: DNA.

2. DNA PROVIDES THE GENETIC CODE

2.1. Structure of DNA

DNA (deoxyribonucleic acid) is a nucleic acid. Nucleic acids are one of the four biological macromolecules essential for life, along with carbohydrates, proteins, and lipids. The structure of DNA was first described in 1953 by James Watson and Francis Crick, whose predictions were assisted by radiographs taken by Rosalind Franklin and suggested by Maurice Wilkins. Despite the complexity of functions required of the genetic code by humans and other species alike, the structure of DNA was found to exhibit surprising simplicity.

DNA is made up of nitrogen-containing bases called nucleotides bound to a sugar-phosphate backbone. The sugar is deoxyribose, a 5-carbon sugar. While the sugar-phosphate backbone remains constant, the nucleotides do not. There are four different nitrogenous bases in DNA: adenine, guanine, cytosine, and thymine, commonly abbreviated as A, G, C, and T, respectively. A and G are classified as purines (double-ringed structures) while C and T are classified as pyrimidines (single-ringed structures). DNA is structured as two chains which form a double helix shape (Figure 1). The two strands are connected via hydrogen bonds between bases on each strand. The bases form bonds in predictable fashion: A always bonds with T, and G always bonds with C. The two strands are thus complementary. These bases make up the genetic code. Genes are transcribed into mRNA (messenger RNA), which is in turn translated into proteins.

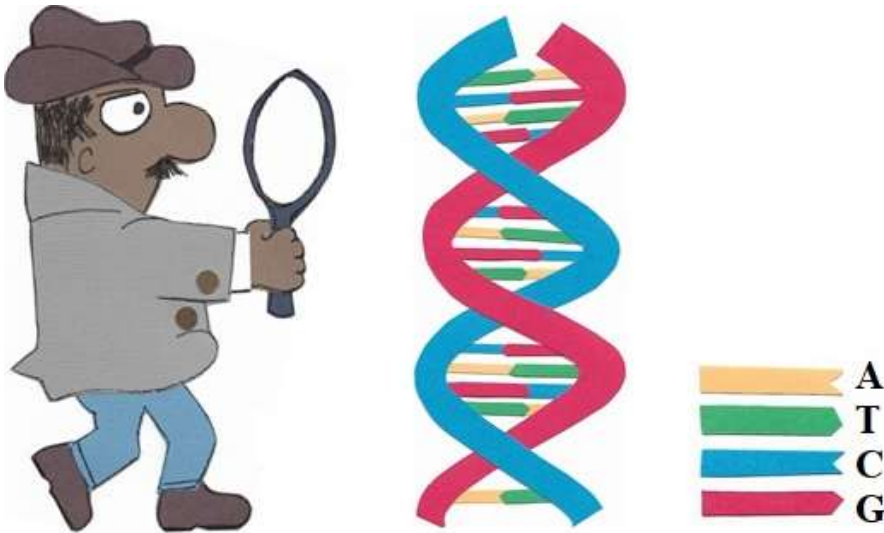


Figure 1. DNA structure. DNA is structured into a double helix with 4 nucleic acid bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Adenine always pairs with thymine while guanine always pairs with cytosine. AT pairs are connected with two hydrogen bonds while GC pairs are connected with three hydrogen bonds.

2.2. DNA Is Packaged into Chromosomes

The roughly 3 billion base pairs of DNA that make up the human genome must be packaged into cells [10]. To accomplish this, DNA utilizes several mechanisms of compaction, which includes involvement of various proteins such as histones [11]. The human genome is arranged into 46 chromosomes. When the chromosomes are at maximal condensation, they can be stained and analyzed microscopically (see Section 6.1.1). The chromosomes are located in the nucleus of the cell. Most cells of the human body have 46 chromosomes packaged in the nucleus. Notable exceptions are the gametes (egg and sperm cells), which contain 23 chromosomes, and mature red blood cells, which do not have a nucleus. Somatic cells (cells that are not gametes) divide through a process known as mitosis, while gametes divide via meiosis. Mitosis and meiosis are similar processes, but meiosis involves two cell divisions as compared to one cell division in mitosis. Both processes precede with DNA replication (doubling). Mitosis follows with a division into two daughter cells each with the same amount of DNA as the parent cell. Meiosis follows with two cell divisions resulting in four daughter cells with half the amount of DNA as the parent cell.

2.3. Chromosomes Come in Pairs

The 46 chromosomes that contain the human genome consist of 23 pairs. One pair is inherited from a person's mother and one pair is inherited from the father. Egg and sperm cells contain 23 chromosomes each, creating a zygote with 46 chromosomes when they come together. The chromosomes are designated as either autosomes or sex chromosomes. The sex chromosomes are X and Y, and they determine sex. Females possess an XX sex chromosome

complement, while males possess an XY chromosome complement. When passing on a sex chromosome to a child, females can only pass on an X chromosome.



Figure 2. Human male karyotype. Normal male karyotype: 46,XY. Karyotype courtesy of the laboratory of Dr. Fern Tsien, Louisiana University Health Sciences Center Department of Genetics, used with permission.

Males can pass on either an X or a Y chromosome, which is why fathers are described as the sex-determining parent. The remaining chromosomes are autosomes, denoted by numbers 1 through 22. They are arranged into karyotypes by descending size, with 1 being the largest, and the sex chromosomes at the end. Chromosome 21 is the smallest chromosome. (Because of the difficulty visualizing chromosomes with early staining methods, chromosomes 21 and 22 were mistakenly put in reverse order. This assignment has remained.) A normal male karyotype is shown in Figure 2.

3. PATTERNS OF INHERITANCE

The four major patterns of inheritance are autosomal dominant, autosomal recessive, X-linked, and mitochondrial. These are each described in more detail in this section. *Autosomal* and *X-linked* both indicate the type of chromosome involved. X-linked genes are located on the X chromosome. Autosomal genes are located anywhere on chromosomes 1 to 22. Traits or disorders can be *dominant* or *recessive*. In Section 2.3, we learned that for any given gene (with the exception of mitochondrial genes), we inherit two copies: one from our mother and one from our father. These alternative gene copies are *alleles*. Alleles can interact in different ways. If one allele masks the other allele, it is a dominant allele. In contrast, a recessive allele is one that is capable of being masked by another allele. The combination of alleles inherited represents an individual's *genotype* while the expression of the genetic make-up represents an individual's *phenotype*. Alleles which differ from the norm may be deemed *mutations* or *polymorphisms*. Mutations typically describe allele variants which are disease-causing, while polymorphisms describe benign allele variants, though technically, the terms can be used

interchangeably. Figures 3-7 show pedigrees of families with genetic deafness of different inheritance patterns. A pedigree is a diagrammatic representation of a family used by genetic counselors and clinical geneticists to record and evaluate genetic traits. In our examples we will use the trait of hearing loss.

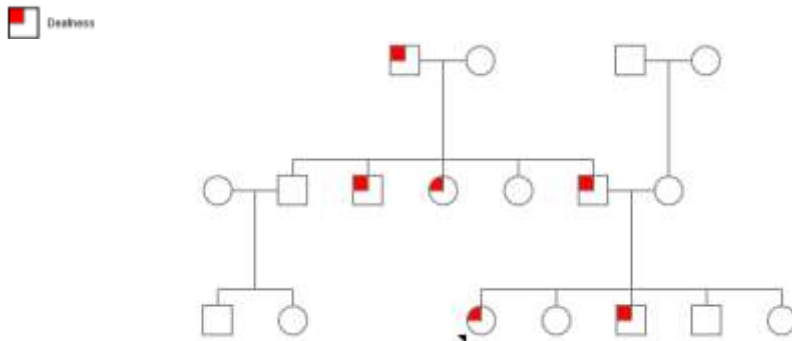


Figure 3. Pedigree of autosomal dominant deafness. Three generations of a family are shown in this pedigree. Males are represented by squares, females by circles; matings are denoted by a horizontal line, offspring by a vertical line. The proband (presenting patient) is indicated with an arrow. Family members affected with deafness are indicated with shading. For someone with autosomal dominant deafness, approximately half of their children would be expected to be deaf. Males and females are affected in roughly equal numbers.

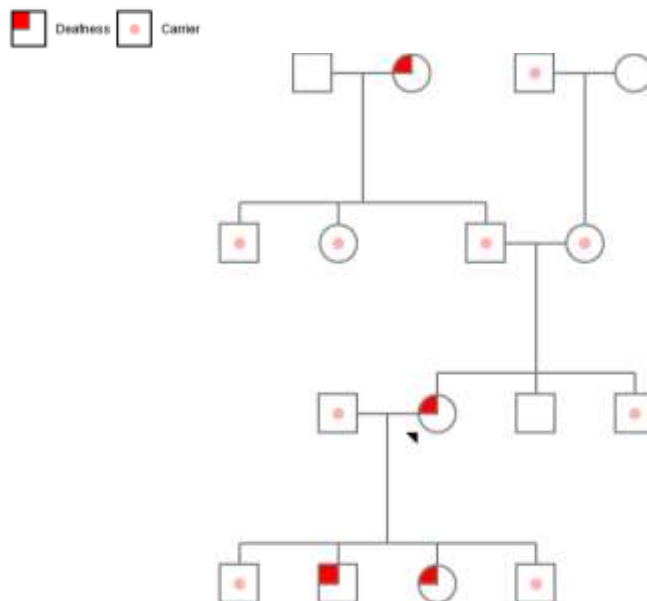


Figure 4. Pedigree of autosomal recessive deafness. Four generations of a family are shown in this pedigree. Males are represented by squares, females by circles; matings are denoted by a horizontal line, offspring by a vertical line. The proband (presenting patient) is indicated with an arrow. Family members affected with deafness are indicated with shading. Unaffected carriers are indicated with a dot. Deaf family members inherited two gene copies for deafness: one from each parent. For unaffected parents who are both carriers for autosomal recessive deafness in the same gene, approximately one-quarter of their children would be expected to be deaf. Males and females are affected in roughly equal numbers.

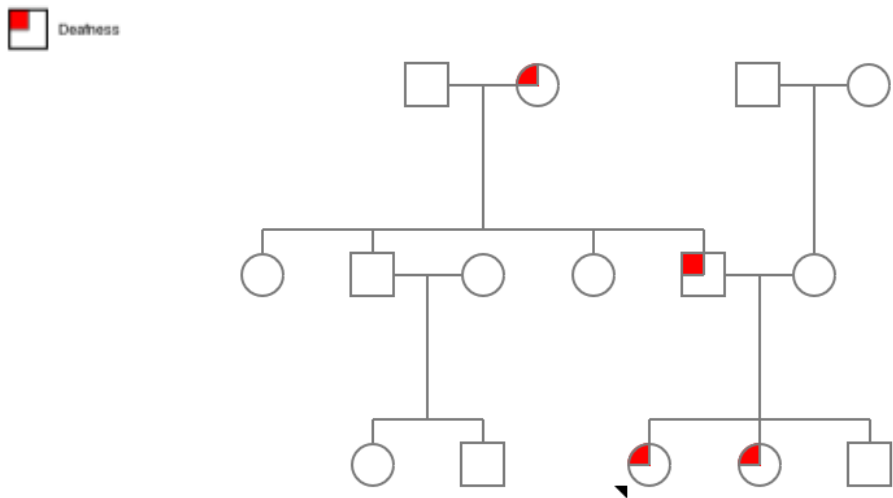


Figure 5. Pedigree of X-linked dominant deafness. Three generations of a family are shown in this pedigree. Males are represented by squares, females by circles; matings are denoted by a horizontal line, offspring by a vertical line. The proband (presenting patient) is indicated with an arrow. Family members affected with deafness are indicated with shading. Affected males will have all daughters affected and no sons affected. For affected females, half of their children will be affected (by probability) regardless of gender. X-linked inheritance will not display male-to-male transmission.

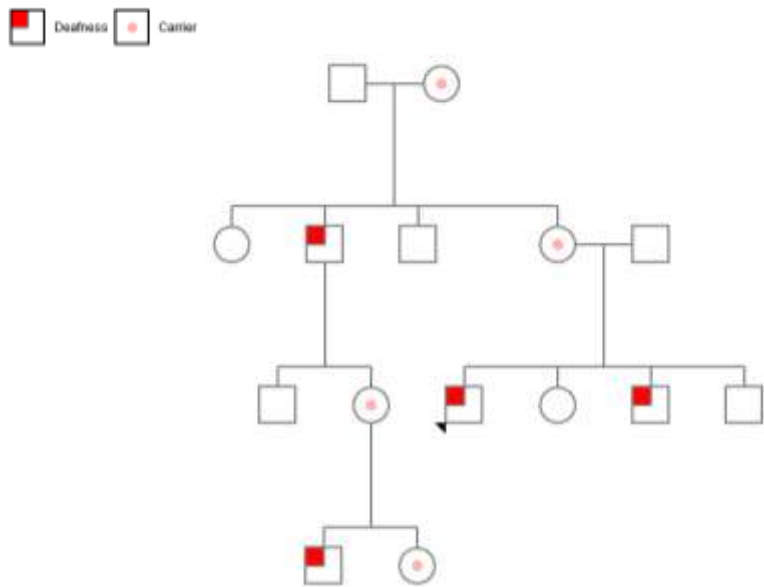


Figure 6. Pedigree of X-linked recessive deafness. Four generations of a family are shown in this pedigree. Males are represented by squares, females by circles; matings are denoted by a horizontal line, offspring by a vertical line. The proband (presenting patient) is indicated with an arrow. Family members affected with deafness are indicated with shading. Unaffected carriers are indicated with a dot. Those affected are disproportionately (sometimes exclusively) male. Carrier females may be affected (usually mildly) if X-inactivation is skewed toward the X chromosome with the normal allele. Affected males will pass the deafness gene to all of their daughters and none of their sons. Affected females will pass the gene on to half of their children (by probability), which is expected to result in all of their sons being affected and all of their daughters being carriers. X-linked inheritance will not display male-to-male transmission.

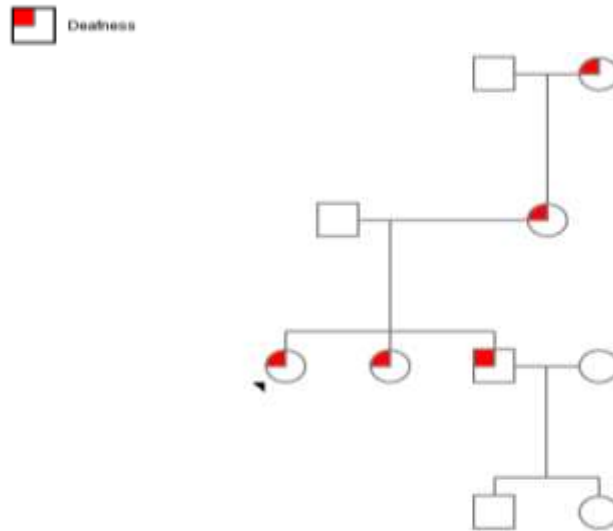


Figure 7. Pedigree of mitochondrial deafness. Four generations of a family are shown in this pedigree. Males are represented by squares, females by circles; matings are denoted by a horizontal line, offspring by a vertical line. The proband (presenting patient) is indicated with an arrow. Family members affected with deafness are indicated with shading. Affected females will pass the gene on to all of their children, while affected males will pass the gene on to none of their children. Males and females are affected in roughly equal numbers.

3.1. Autosomal Dominant

When a given trait or condition displays an autosomal dominant inheritance pattern, only one copy of a gene is necessary to cause the given trait. A person with autosomal dominant hearing loss will be expected to have received one copy of a hearing loss gene from one parent and a normal copy from the other parent. A parent with a mutation for autosomal dominant hearing loss will have a 50% chance of passing on the mutation to each child (Figure 8). Since the trait is dominant, we expect that each child receiving this allele will be affected with hearing loss. However, this is not always the case because some autosomal dominant traits exhibit reduced penetrance. If a trait is fully penetrant, all individuals who receive the allele will exhibit the trait. If the trait has reduced penetrance, there will be individuals who carry the allele but do not possess the trait. It is not clear why this occurs, but it may be due to the influence of other genes.

In a minority of cases of autosomal dominant hearing loss, the hearing loss arises due to a new mutation in the patient. When this occurs, neither parent will carry the mutation, and the odds of having another child with the same mutation are very low. This is why genetic testing of parents is necessary to estimate recurrence risks. While new mutations can occur in any type of disorder, they are seen far more frequently in autosomal dominant disorders because only one mutation is necessary.

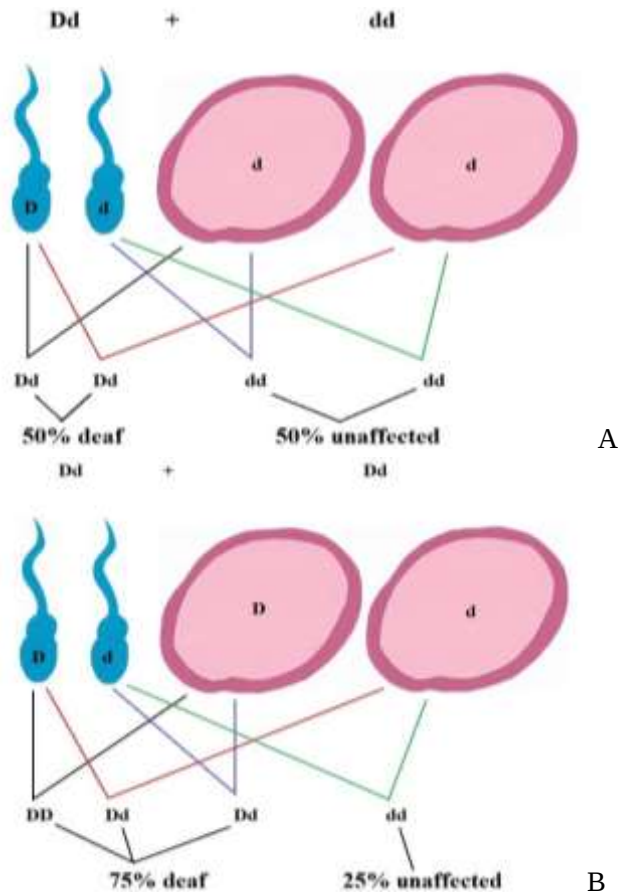


Figure 8. Autosomal dominant inheritance: risk to offspring. Autosomal dominant inheritance most commonly occurs when one parent is affected. In 8A, the father is affected with autosomal dominant deafness. We will use capital “D” and lowercase “d” to represent the dominant and recessive alleles for the gene in question, respectively. Since this gene is autosomal dominant, “D” is the deafness allele and “d” is the normal allele. The deaf father carries a “D” allele and a “d” allele, and therefore his sperm cells will be one of two varieties. Each of his children will inherit either a “D” allele or a “d” allele from him. There is a 50% chance of each of these possibilities for each child. The unaffected mother has two “d” alleles, and thus all of her children will inherit the “d” allele from her. Since the “D” allele is dominant and will result in deafness, 50% of the children born to this couple will be expected to exhibit deafness. In 8B, both parents have autosomal dominant deafness for the same gene. Both of them have one “D” allele and one “d” allele they can pass on to their children. When we evaluate each of the four combinations in which these alleles can come together, each child born to this union would have a 75% chance of being deaf (DD or Dd) and a 25% chance of being unaffected (dd).

3.2. Autosomal Recessive

A person with autosomal recessive hearing loss will have two copies of a mutation for the involved gene. Unlike dominant conditions, two copies are required for a recessive condition to appear. Those who carry one copy of a recessive gene are known as carriers because they do not show outward signs of the mutation they carry. The frequent mechanism of inheritance for an individual with autosomal recessive hearing loss is two unaffected parents who each carry a mutation for the causative gene. This is by far the most common scenario in genetic

hearing loss, and explains in large part why more than 90% of children with permanent hearing loss are born to hearing parents [12]. Each child of parents who are carriers for mutations in the same gene will have a 25% chance of inheriting both copies, and therefore being affected. They will have a 50% chance of being an unaffected carrier (Figure 9). While new mutations can occur in recessive conditions, this is seen far less frequently because it would be unusual for two new mutations to occur in the same gene. Another slightly more probable mechanism has been observed in autosomal recessive disorders, whereby an individual receives one copy of a disease gene from one parent and experiences a new mutation in the same gene inherited from the other parent.

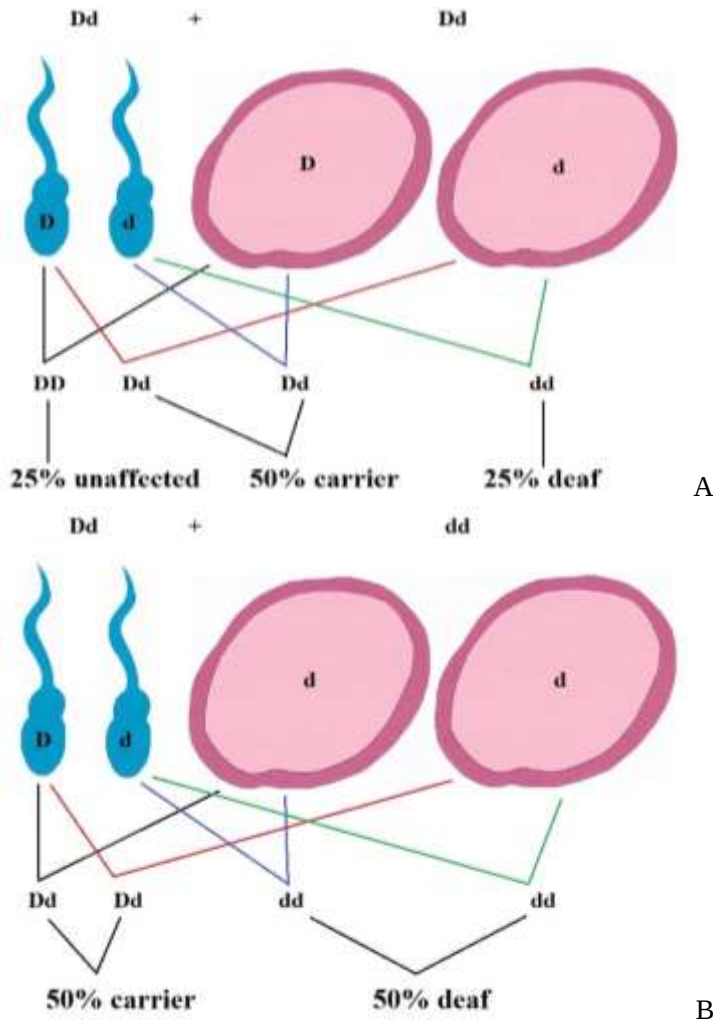


Figure 9. Autosomal recessive inheritance: risk to offspring. In autosomal recessive inheritance, the deafness gene is the lowercase “d”. Deafness will only manifest if an individual carries both copies of the “d” deafness allele. Autosomal recessive inheritance most commonly occurs when two unaffected parents are carriers (9A). Both parents have the genotype Dd and can pass on either allele to each child. The four combinations possible from this union lead to a 25% chance of a deaf child (dd), a 50% chance of a child who is a carrier (Dd), and a 25% chance of an unaffected child (DD) from each conception. In 9B, the mother is affected with autosomal recessive deafness and the father is an unaffected carrier for the same gene. In this mating, each child has a 50% chance of being deaf (dd) and a 50% chance of being an unaffected carrier (Dd).

3.3. X-Linked

X-linked genes are inherited on the X chromosome, and are thus also known as sex-linked genes because they are inherited differently in males and females. Males are far more likely to exhibit an X-linked disorder, and they tend to be more severely affected than their

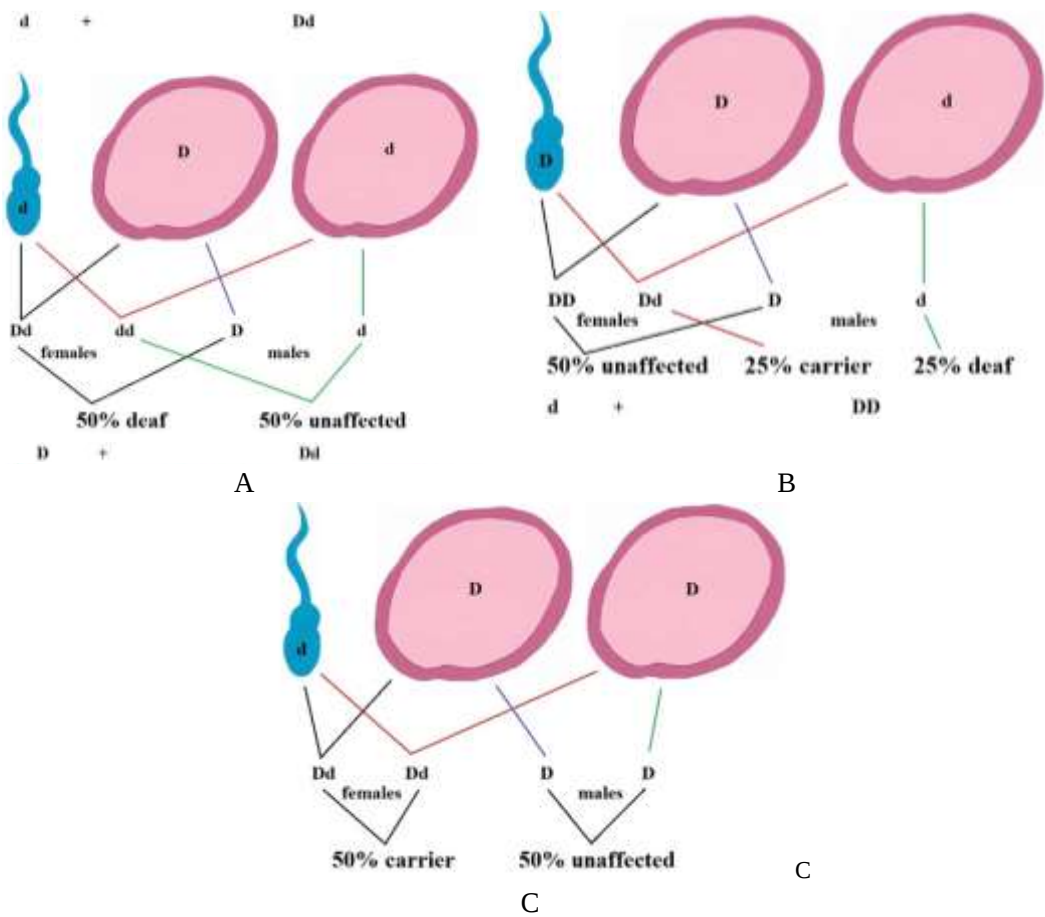


Figure 10. X-linked inheritance: risk to offspring. With X-linked inheritance, females have two X chromosomes, and therefore two alleles, while males have one X chromosome and one allele. 10A demonstrates X-linked dominant inheritance with an affected mother. The deafness allele is capital “D”. The mother can pass on “D” or “d” to each of her children. The father can only pass on “d” to his daughters; he does not pass on an allele from the X chromosome to his sons because his sons will inherit a Y chromosome from him. Each child from this mating will have a 50% chance of being affected (Dd for daughters and D for sons) and a 50% chance of being unaffected (dd for daughters and d for sons). 10B illustrates X-linked recessive inheritance with a carrier mother (Dd) and an unaffected father (DD). Since this is recessive inheritance, “d” is the deafness allele, which will only manifest in the absence of a “D”. Sons can receive either “D” or “d” from their mother, and thus have a 50% chance of being deaf and a 50% chance of being unaffected. Since daughters can only receive a normal allele from their father, they will have a 50% chance of being a carrier (Dd) and a 50% chance of being unaffected (DD). Combining all offspring together for this mating, we expect 25% to be deaf, 25% to be carriers, and 50% to be unaffected. Finally in 10C, we have X-linked recessive inheritance with a deaf father (d) and an unaffected (noncarrier) mother (DD). In this mating all daughters will be carriers (Dd) and all sons will be unaffected (D).

female counterparts. Males are more vulnerable to X-linked disorders because they only possess one X chromosome. By having one X chromosome, males only have one copy of each gene located on the X-chromosome. Females have two X chromosomes, so a second allele could potentially mask a mutation on the other allele. For males, X-linked traits are maternally-inherited because males only inherit X chromosomes from their mothers. Likewise, a male with an X-linked disorder will pass this trait on to all of his daughters and none of his sons (Figure 10). X-linked genes can also be dominant or recessive, but some clinicians prefer not to use these descriptors because dominance and recessiveness are not as clear-cut with X-linked inheritance. When considering males, they will be affected with an X-linked disorder if they receive a gene with a mutation associated with a disorder. Since males will only have one copy of this gene, it is not particularly relevant to their condition whether or not it is dominant or recessive (though it may have relevance in regards to recurrence risks to offspring).

Dominance and recessiveness have greater relevance with females, who have two X chromosomes. It would therefore be expected that a female would be affected with an X-linked dominant disorder if she carries one copy of the mutation, and would be affected with an X-linked recessive disorder only if she carries two copies of the mutation. However, there are cases of unaffected or mildly affected females with a mutation for an X-linked dominant disorder, as well as cases of affected females for an X-linked recessive disorder who carry only one copy of a mutation. This is due to a phenomenon known as skewed X-inactivation. During development, one of the X chromosomes in every cell of a female's body is inactivated. The X chromosome inactivated in each cell is largely random. As a result, females carrying one copy of an X-linked disease gene display wide variability depending on the proportions of inactivation for each X chromosome. It is because of skewed X-inactivation that an X-linked disorder that is dominant or recessive may not always appear to be inherited in a family as expected. It should also be noted that some X-linked disorders are actually more common in females. These tend to be X-linked dominant disorders with a severe clinical presentation. An example is Rett syndrome, characterized by severe developmental delay and autistic features. Rett syndrome is inherited on the X chromosome, but it is observed almost exclusively in females because it is lethal to males *in utero*. A similar outcome occurs in many autosomal dominant disorders when two mutation copies are inherited.

3.4. Mitochondrial

Mitochondria are cellular organelles primarily responsible for energy production, hence their nickname “powerhouse of the cell.” The mitochondria are located outside the nucleus, where the chromosomes are located (Figure 11). Mitochondria have their own genome of only 37 genes located on one circular chromosome whose structure and function are reminiscent of a bacterial chromosome. Mitochondria are found in many cells throughout the body, including egg cells, but they are not found in mature sperm cells. Because they are not in sperm cells, mitochondrial genes are exclusively inherited maternally. A mother with a mutation in a mitochondrial gene will pass on the mutation to all of her children, while a man with a mitochondrial mutation will not pass it on to any of his children (Figure 12). The

primitive mitochondrial genome does not have the sophisticated DNA repair mechanisms observed in the nuclear genome, and thus, is highly prone to mutations.

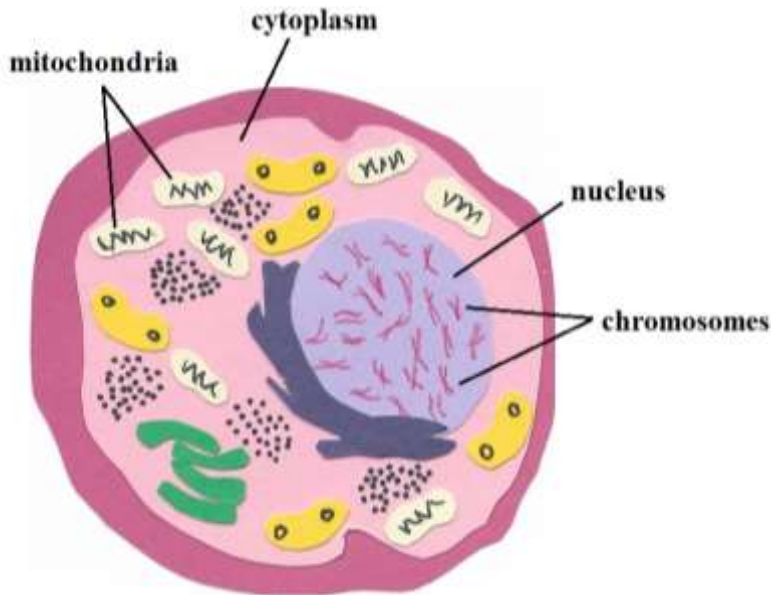


Figure 11. Human Cell. This figure illustrates the position of the nuclear and mitochondrial genomes in the human cell. The nucleus contains 46 chromosomes (23 chromosomes in gametes), which hold nearly all of the approximately 20,000 human genes. Mitochondria are organelles located in the cytoplasm, outside of the nucleus. Mitochondria have their own genome consisting of 37 genes. The inheritance of these genes does not follow the same inheritance pattern as nuclear genes. Rather, mitochondrial genes are inherited exclusively from the mother, as they are found in egg cells but not in sperm cells.

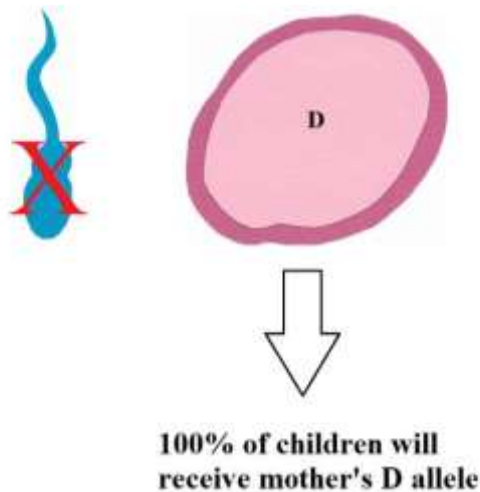


Figure 12. Mitochondrial inheritance: risk to offspring. Since mature sperm cells do not contain mitochondria, a father's genotype for a mitochondrial gene has no effect on his offspring. A mother who is affected with a mitochondrial gene will pass this on to all of her children. (Though not discussed in this chapter, mitochondrial inheritance is sometimes more complex than this. An individual can carry mitochondria which are all of the same genotype, known as *homoplasmy*, or mitochondria with different genotypes, known as *heteroplasmy*. Homoplasmy is demonstrated here.)

4. SYNDROMIC HEARING LOSS

A syndrome is a disease, disorder, or condition that is associated with a particular set of signs, symptoms, or characteristics. Though many syndromes have a genetic etiology, this is not always the case.

Syndromic hearing loss is a syndrome which typically includes hearing loss as one of its clinical features. While many syndromes are characterized by distinct facial or physical features, bear in mind that clinical features are not always readily visible. Below is a brief overview of selected syndromes with hearing loss as a clinical feature in many patients.

4.1. Syndromes with Autosomal Dominant Inheritance

4.1.1. Stickler Syndrome

Stickler syndrome has an incidence of 1 in 7,500 to 9,000. It is associated with visual problems, which may include severe nearsightedness, glaucoma, cataracts, and retinal detachment. There is a characteristic flattened facial appearance, which often includes a large tongue, small lower jaw, and cleft palate. Joints are very flexible. Conductive, sensorineural, or mixed hearing loss may be seen, as the middle ear and inner ear can be affected [13, 14].

Stickler syndrome is inherited in an autosomal dominant fashion, though a small number of cases are inherited in an autosomal recessive fashion or are due to new mutations. It is caused by mutations in various genes which code for collagen proteins: *COL2A1*, *COL9A1*, *COL11A1*, and *COL11A2* [14]. The abnormal collagen causes the bones of the face to not form properly and leads to hyperflexibility in the joints. Breathing and feeding difficulties result from the combination of a large tongue and small lower jaw. Hearing loss is usually present at birth and gets worse over time [13, 14].

4.1.2. CHARGE Syndrome

CHARGE syndrome is a serious medical disorder characterized by a number of physical and developmental problems and distinct facial features. It has an incidence of 1 in 10,000. It was originally named for what was believed to be its major features: Coloboma, Heart defects, Atresia of choanae, Retardation of growth and development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness. Many patients are born with life-threatening birth defects, such as heart defects and breathing problems. Intelligence is variable but most patients have severe intellectual disability. Choanal atresia or stenosis (narrow or blocked passages from the back of the nose to the throat) cause breathing problems. Cranial nerve abnormalities may be present, especially of nerves I, VII, and IX/X, leading to absent or decreased sense of smell, facial palsy, and swallowing difficulties, respectively. Coloboma of the eye (cleft of the iris, retina, choroids, macula, or disc) may be associated with vision loss. Cleft lip and/or palate, kidney problems, and tracheo-esophageal fistula may be present [15, 16].

The outer, middle, and inner ear can all be affected, and thus hearing loss may be conductive, sensorineural, or mixed. Severity of hearing loss ranges from mild to profound and may be progressive. Outer ear abnormalities reported include a short, wide pinna with little or no lobe, triangular concha, decreased cartilage leading to a floppy ear, and a missing

piece of helix, giving the appearance that a piece of the helix has been snipped. Malformed ossicles have been reported in the middle ear, as well as chronic, recurrent otitis media with effusion. Mondini defects and small or absent semicircular canals may occur in the inner ear [15, 16].

Characteristic facies are a square face with a broad prominent forehead, arched eyebrows, ptosis, flat midface, small mouth, facial asymmetry, and prominent nasal bridge with square root. A common physical feature is a palmar crease in the shape of a hockey stick [15, 16].

CHARGE syndrome is caused by a mutation in the *CHD7* gene. *CHD7* helps regulate gene expression during development. A mutation in this gene causes disrupted development, resulting in many physical abnormalities. Only about 2/3 of patients test positive for a *CHD7* mutation, so there may be other causative genes that have not been identified. Diagnosis is most frequently made clinically. Inheritance pattern is autosomal dominant, but almost all cases are due to new mutations. Recurrence risks are therefore very low for parents with an affected child [17-20].

4.1.3. Cornelia de Lange Syndrome

The exact incidence of Cornelia de Lange syndrome is unknown, but it is estimated at 1 in 10,000 to 30,000. Clinical presentation is variable from one patient to the next, but there are many physical signs associated with Cornelia de Lange syndrome, including: severe to profound intellectual disability and growth retardation, microcephaly, hirsutism, confluent eyebrows, small nose with anteverted nares, downturned upper lip, micrognathia, long curly eyelashes, cleft palate, cardiac defects, and severely malformed upper limbs, possibly with missing fingers or toes and webbed toes. Auditory system defects may include low-set auricles and small external auditory canals. Hearing loss is variable and may be conductive, sensorineural, or mixed [21, 22].

Cornelia de Lange syndrome has been reported to be caused by mutations in five different genes: *NIPBL*, *SMC1A*, *HDAC8*, *RAD21*, and *SMC3* [23-26]. Mutations in *NIPBL* are responsible for more than half of cases. These genes code for proteins important for prenatal growth development. The cause is unknown in about 30% of cases, suggesting there are more genes yet to be identified. Inheritance pattern is typically autosomal dominant, though approximately 5% of cases are X-linked dominant. Most cases are due to new mutations, and thus occur in patients with no family history [23-26].

4.1.4. Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF2) is a disorder featuring growth of benign tumors in the nervous system, primarily in the brain. In many patients this includes growths on one or both vestibulocochlear nerves. These vestibular schwannomas/acoustic neuromas lead to the same sequelae as patients without NF2: neural hearing loss, tinnitus, and vertigo. A notable difference is that a patient with NF2 is likely to be affected bilaterally, though not necessarily at the same time. In those affected bilaterally, loss of VIIIth nerve function is common [27, 28]. If loss of VIIIth nerve function is bilateral, the patient is not a cochlear implant candidate but may pursue an auditory brainstem implant. However, auditory brainstem implant outcomes have been reported to be poorer for NF2 patients compared with non-NF2 patients [29]. Other NF2 tumors may cause vision changes, peripheral numbness or weakness, or fluid in the brain. The incidence of NF2 is estimated at 1 in 33,000. Signs often show up in childhood, though they can develop at any age [27, 28].

NF2 is caused by mutations in the *NF2* gene, which codes for a protein important for insulating neurons [30]. NF2 is an autosomal dominant disorder, but it is inherited from an affected parent in only half of cases. The remainder are due to new mutations. NF2 should not be confused with the more common neurofibromatosis type 1 (NF1, incidence of 1 in 4,000), which is not typically associated with hearing loss. Physical signs of NF1 include café-au-lait spots (areas of darker pigmentation on the skin), Lisch nodules (growths on the iris of the eyes), axillary and inguinal freckling, subcutaneous neurofibromas, and optic gliomas, which may lead to vision loss [27, 28].

4.1.5. Branchio-oto-Renal Syndrome

Branchio-oto-renal syndrome affects the neck (branchio), the ears (oto), and the kidneys (renal). Estimated prevalence of this syndrome is 1 in 40,000. This syndrome arises from a disruption in the development of tissues in the neck. Primary physical signs include branchial cleft cysts, fistulae between the skin of the neck and the throat, preauricular pits or tags, malformed or misshapen pinnae, middle or inner ear structural defects, and abnormal kidney structure and function [31, 32]. Surgery may be warranted to treat cysts or fistulae of the neck. Dialysis may be needed to treat kidney disease. Hearing loss can vary in severity, and may be conductive, sensorineural, or mixed. Approximately 2% of the profoundly deaf are thought to have branchio-oto-renal syndrome [33].

Mutations in three different genes have been reported to cause branchio-oto-renal syndrome: *EYA1*, *SIX1*, and *SIX5*, with *EYA1* being responsible for about 40% of cases [34-36]. The resultant proteins from these genes are involved in embryonic development. Branchio-oto-renal syndrome is inherited in an autosomal dominant fashion. About 10% of cases are due to new mutations [37].

4.1.6. Waardenburg Syndrome

Waardenburg syndrome consists of sensorineural hearing loss along with specific physical features, including a white forelock; pale blue eyes, different-colored eyes (complete heterochromia), or two different colors in the same eye (partial heterochromia); widely-spaced eyes (hypertelorism); lateral displacement of medial canthi; prominent broad nasal root; and hypertrichosis of the medial part of the eyebrows [38, 39]. Its prevalence is estimated at 1 in 42,000 [39]. Hearing loss severity can range from mild to profound, and is usually bilateral, though unilateral cases have been reported [40]. Some individuals will show physical features but have normal hearing. About 2% of cases of profound congenital hearing loss are attributable to Waardenburg syndrome [38].

There are four distinct types of Waardenburg, with types I and II being the most common. Physical features vary between types but also between individuals of the same type. For example, hypertelorism is commonly seen in type I and not in type II, while hearing loss is more common in type II than in type I [41]. Waardenburg syndrome exhibits reduced penetrance, meaning individuals who carry a mutation for Waardenburg syndrome do not always manifest the disorder. These individuals can, however, pass it on to their children where it may be fully penetrant in the offspring. This syndrome also demonstrates variable expressivity, meaning that individuals with the same mutation may have different clinical presentations. This can even occur in members of the same family. Inheritance pattern is typically autosomal dominant, but a small number of cases are due to autosomal recessive inheritance or new mutations. Several genes have been implicated in Waardenburg syndrome,

many of which are involved in melanocyte development [42]. The reader is referred to OMIM (Online Mendelian Inheritance in Man) at <https://www.omim.org/> for a current review [43].

4.1.7. Treacher Collins Syndrome

Treacher Collins syndrome has an incidence of 1 in 50,000 live births. This condition arises from abnormal development of facial bones and tissues. Characteristic facial features include down-slanting palpebral fissures, notched lower eyelids, micrognathia, underdevelopment or absence of cheekbones and eye socket floor, and cleft palate. About half of individuals with Treacher Collins syndrome have conductive hearing loss due to atresia, microtia, and/or malformed ossicles [44, 45].

Most cases of Treacher Collins syndrome display autosomal dominant inheritance, but less than 2% show autosomal recessive inheritance. Approximately 60% of autosomal dominant cases are due to new mutations. More than 80% of cases are due to the *TCOF1* gene, with a small minority due to *POLR1C* and *POLR1D* [46, 47]. These genes play roles in the development of facial bones and tissues. Variable expressivity is seen in Treacher Collins syndrome ranging from unnoticeable to severe facial malformation [48]. Because of this, it should not be assumed that a patient's Treacher Collins syndrome is due to a new mutation when neither of the parents exhibit signs of the condition. Patients and their parents should receive genetics evaluations if the families desire accurate estimates of recurrence risks.

4.1.8. Crouzon Syndrome

Crouzon syndrome is the most common craniosynostosis disorder, with an incidence of 1 in 60,000 live births. Facial features include midface hypoplasia, shallow orbits with protruding eyes, strabismus, beaked nose, underdeveloped upper jaw, and large forehead. Dental problems and cleft lip and palate are also common. Conductive hearing loss occurs due to deformed or narrow external ear canals, narrowed internal auditory canals, chronic otitis media with effusion, and poor Eustachian tube function [49, 50].

Crouzon syndrome is caused by mutations in the *FGFR2* gene. This gene has many functions, including signaling cellular differentiation during embryonic development [50]. Mutations lead to premature fusion of sutures in the skull. Inheritance for Crouzon syndrome is autosomal dominant, though approximately 25% of cases are due to new mutations [51].

4.1.9. Apert Syndrome

Apert syndrome is a craniosynostosis disorder with many similarities to Crouzon syndrome. Reported incidence and prevalence data vary, but Apert syndrome affects approximately 1 in 70,000 live births with a prevalence of about 1 in 100,000. Common physical features are frontal bossing, midface hypoplasia, protruding eyes, strabismus, low-set ears, syndactyly, hyperhidrosis, oily skin with severe acne, patches of missing hair in the eyebrows, and cleft lip and palate. Shallow eye sockets can cause vision problems. Cognitive abilities range from normal to mild to moderate intellectual disability. Conductive hearing loss and recurrent otitis media are common [49, 52].

Like Crouzon syndrome, Apert syndrome is caused by mutations in the *FGFR2* gene and has an autosomal dominant inheritance pattern. Unlike Crouzon syndrome, virtually all cases of Apert syndrome are due to new mutations [49, 52].

4.2. Syndromes with Autosomal Recessive Inheritance

4.2.1. Pendred Syndrome

Pendred syndrome is a disorder associated with sensorineural hearing loss and thyroid goiter. Exact incidence is unknown but it is estimated to affect 1 in 13,000 to 15,000 people. Thyroid goiter is most likely to appear between late childhood and early adulthood, and it usually does not affect thyroid function. Severe to profound sensorineural hearing loss is typically congenital and may be progressive or fluctuating. Enlarged vestibular aqueduct is typically present, which may cause balance disturbances [53-55]. About half of individuals with Pendred syndrome have a Mondini malformation [55].

Pendred syndrome is caused by mutations in the *SLC26A4* gene, which codes for pendrin, a protein that transports anions in and out of cells. While its role is not fully understood, it is known to be important for normal functioning of the thyroid and inner ear [56]. Inheritance of Pendred syndrome is autosomal recessive. Mutations in *SLC26A4* are also responsible for some cases of nonsyndromic hearing loss. Altogether this gene is thought to account for 5 to 10% of hereditary deafness [57, 58].

4.2.2. Usher Syndrome

Usher syndrome is a condition of combined hearing loss and vision loss, sometimes accompanied by vestibular dysfunction. Its prevalence worldwide is estimated at 4 per 100,000, but it is reported to be much more common in certain populations, particularly in Ashkenazi Jewish and Louisiana Acadian populations [59, 60]. Though rare, Usher syndrome is responsible for about half of all concurrent deafness and blindness in adults [61, 62]. There are three types of Usher syndrome, with type I being the most severe. Vision loss first presents as night blindness and later progresses to retinitis pigmentosa [59].

The typical course for type I Usher syndrome is congenital bilateral profound sensorineural deafness, with progressive vision loss beginning around 10 years of age [59]. The vision deteriorates to blindness by early adulthood. There is also an absence of vestibular function, which frequently goes unnoticed. Mothers of children with Usher syndrome commonly report they were late to begin walking, often 18 months to 2 years of age. As the child grows and develops, the central nervous system adapts to this lack of vestibular function. A typical presentation of type II Usher syndrome is congenital moderate to severe sensorineural hearing loss, and vision loss beginning in adolescence [63]. Progression to blindness commonly occurs in the 30s. Vestibular function remains intact. Type III is the mildest form of Usher syndrome. It accounts for only 2-4% of cases worldwide, but up to 40% of cases in the Finnish population [63]. Hearing loss is progressive and typically less severe. Onset of both hearing loss and retinitis pigmentosa is variable. Vestibular function among patients is also variable, with everything from normal to absent vestibular function reported. A summary of Usher syndrome clinical presentations by type is shown in Table 1.

Table 1. Usher syndrome clinical presentations by type

	Type I	Type II	Type III
Hearing Loss	Profound	Severe	Progressive
Vestibular function	Absent	Normal	Variable
Onset of blindness (decade)	First	Second	Variable

Usher syndrome is an autosomal recessive disorder. It is thought to be more common in certain populations, such as the Louisiana Acadians, due to the founder effect, illustrated in Figure 13 [60]. A founder effect results when a small group of individuals become “founders” of a new population. This new founder population becomes isolated, either geographically or culturally, from other populations for several generations. The ultimate effect is that they become genetically isolated. Since the original founders were from a very small group, they may not be genetically diverse. After many generations certain traits or disorders may be amplified. In the case of the Louisiana Acadians, their roots can be traced back to French descendants of Canadian Nova Scotia Acadians. A few hundred of these descendants migrated to southern Louisiana in the 1700s. At this writing there are 11 genes associated with Usher syndrome and 3 genetic loci [63]. A locus is a fixed position on a chromosome, in this case where a gene is located. A locus (plural loci) may be described in association with a certain trait or condition prior to the identification of the responsible gene. Hence, there will likely be more genes recognized as causative for Usher syndrome. Genes responsible for Usher syndrome code for proteins of different classes and families. For more information on the functions of these proteins, the reader is referred to Yan and Liu, 2010 [63]. The genes involved in Usher syndrome are listed in Table 2.

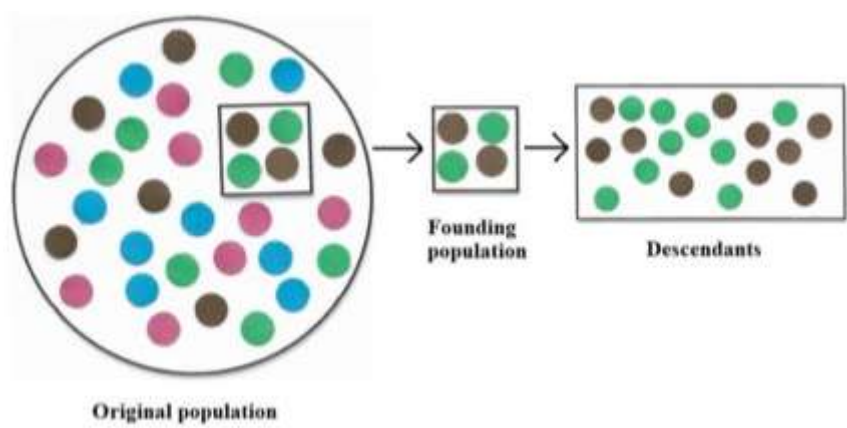


Figure 13. Founder effect. The founder effect is observed when a population is derived from a founding population which consisted of relatively few members. This figure illustrates the concept of the founder effect. A few members of the original larger population broke off and formed a new colony. Due to the small starting population size, the colony has reduced genetic variation and a non-random sample of the genes from the original population. After many generations of geographic and cultural isolation, gene variants which were once rare have propagated and become relatively common. As a result, some diseases are found more frequently in these groups than in other populations, or they have distinct clinical or genetic features due to unique mutations.

Table 2. Genes involved in Usher syndrome

Type I	Type II	Type III
MYO7A	USH2A	USH3A
USH1C	ADGRV1	HARS
CDH23	WHRN	
PCD15		
SANS		
CIB2		

4.2.3. Jervell and Lange-Nielsen Syndrome

Jervell and Lange-Nielsen syndrome affects 1.6 to 6 per 1,000,000 people. Though rare, it has been suggested that up to 3 out of 1,000 people born deaf have Jervell and Lange-Nielsen syndrome [64]. It is characterized by congenital bilateral profound sensorineural hearing loss and cardiac defects. Since the cardiac issues are not present at birth, a proper diagnosis is often late or missed altogether. The first physical signs of cardiac problems are irregular heartbeats in early childhood, which may lead to episodes of fainting, or syncope. Long QT syndrome, a serious condition causing heart muscle to take longer than usual to recharge between beats, may be present [65]. There is a risk of cardiac arrest and sudden death in patients with this syndrome. Treatment may involve beta-adrenergic blockers for long QT syndrome and implantable cardioverter defibrillators (ICDs) for patients with a history of cardiac arrest [66].

Jervell and Lange-Nielsen syndrome is caused by mutations in either the *KCNQ1* or *KCNE1* genes. *KCNQ1* is responsible for 90% of cases while *KCNE1* is responsible for 10% of cases [66]. These genes code for potassium ion channels. Mutations in one of these genes lead to faulty potassium ion channels, which disrupts the usual flow of ions through the inner ear and cardiac muscle. The heart and inner ear are the areas of the body with the greatest utilization of potassium ions. Therefore, these areas are most affected by the faulty channels [66]. Jervell and Lange-Nielsen syndrome is an autosomal recessive disorder.

4.3. Syndrome with X-Linked Inheritance: Alport Syndrome

Alport syndrome is characterized by hearing loss, kidney disease, and eye abnormalities, which may include a decrease in vision in a minority of patients [67]. It has a reported incidence of 1 in 50,000 [68]. Hearing loss varies from mild to severe sensorineural hearing loss, often sloping, and may be progressive. Typical age of onset for hearing loss is late childhood to early adolescence. More than half of patients with Alport syndrome have hearing loss, with males much more likely than females to exhibit this clinical feature. Kidney disease is preceded by blood in the urine (hematuria). As kidney disease progresses, proteinuria and hypertension develop. Many patients develop end-stage renal disease and require dialysis and kidney transplantation. Males are almost always more severely affected than females. Eye abnormalities may include anterior lenticonus (an abnormally-shaped lens), cataracts, corneal erosions, and retinal thinning [69].

Alport syndrome is caused by mutations in *COL4A3*, *COL4A4*, and *COL4A5*, genes coding for type IV collagen [70, 71]. This type of collagen is an important structural component in the glomeruli of the kidneys. Approximately 80 to 85% of cases are inherited in an X-linked dominant fashion, explaining why males are affected more frequently and more severely than females. About 15% of cases display an autosomal recessive inheritance pattern and 1% show an autosomal dominant pattern [72].

4.4. Syndromes with Mitochondrial Inheritance: MELAS and MERRF

MELAS and MERRF are two syndromes caused by mitochondrial mutations. The exact incidences of these syndromes are unknown, but they are both very rare. As with all

mitochondrial disorders, they are inherited maternally, though they can be due to new mutations. MELAS and MERRF both affect many systems of the body, especially the muscles, brain, and nervous system, cell types rich in mitochondria [73, 74]. Severity is variable, sometimes even amongst affected family members. Sensorineural hearing loss can appear in both syndromes. They are named after their most prominent features: *MELAS* (Mitochondrial encephalomyopathy, Lactic acidosis, and Stroke-like episodes); *MERRF* (Myoclonic epilepsy with Ragged red fibers). Muscle pain/weakness/twitches and seizures are common features [73, 74].

4.5. Down Syndrome: The Most Common Genetic Syndrome

Down syndrome occurs in 1 out of every 700 live births, making it the most common genetic syndrome [75]. Down syndrome differs from the other genetic syndromes discussed in this chapter in that it is a cytogenetic, or chromosomal disorder. Also known as trisomy 21, Down syndrome is caused by an extra chromosome 21. An individual with Down syndrome will therefore have a chromosome complement of 47 in every cell, as opposed to the typical 46 chromosomes. This is essentially a duplication of every gene on chromosome 21. (A minority of cases display mosaicism, in which some cells have 47 chromosomes and some cells have 46 chromosomes. These patients tend to be affected more mildly.) Chromosome 21 has over 700 genes, 200 to 300 of which code for proteins [76]. Down syndrome is one of the few trisomies that is compatible with life, owing to the fact that there are fewer genes on chromosome 21 than any other autosome. (The Y chromosome, a sex chromosome, contains about 200 fewer genes.)

Down syndrome consists of intellectual disability, characteristic facial and physical features, and heart defects in about half of patients. Physical features include hypotonia, flat facial profile, epicanthal folds, up-slanting palpebral fissures, small low-set ears with folded helix, shortened limbs, and transpalmar crease [77]. Gastrointestinal problems associated with intestinal or esophageal blockages may occur. There is an increased risk of developing heart disease and leukemia. Hearing loss is common, especially conductive hearing loss owing to small ear canals and short Eustachian tubes. These attributes frequently lead to cerumen blockage and chronic otitis media with effusion, respectively. Sensorineural hearing loss is also not uncommon in individuals with Down syndrome, with permanent hearing loss being reported in 25% of patients [78].

Down syndrome occurs during a nondisjunction event during cell division, whereby the homologous pair of chromosome 21s do not segregate appropriately into each daughter cell. This nondisjunction can occur via three different mechanisms: during meiosis of the egg cell, during meiosis of the sperm cell, or during postzygotic mitosis. Nondisjunction during meiosis of the egg cell is the most common mechanism, and is illustrated in Figure 14. It is unknown why nondisjunction occurs, but it happens much more frequently in egg cells as a woman ages. Advanced maternal age is therefore a major risk factor for Down syndrome. It can be diagnosed prenatally through cytogenetic testing via maternal blood sample (cell-free fetal DNA), amniocentesis, or chorionic villus sampling (CVS).

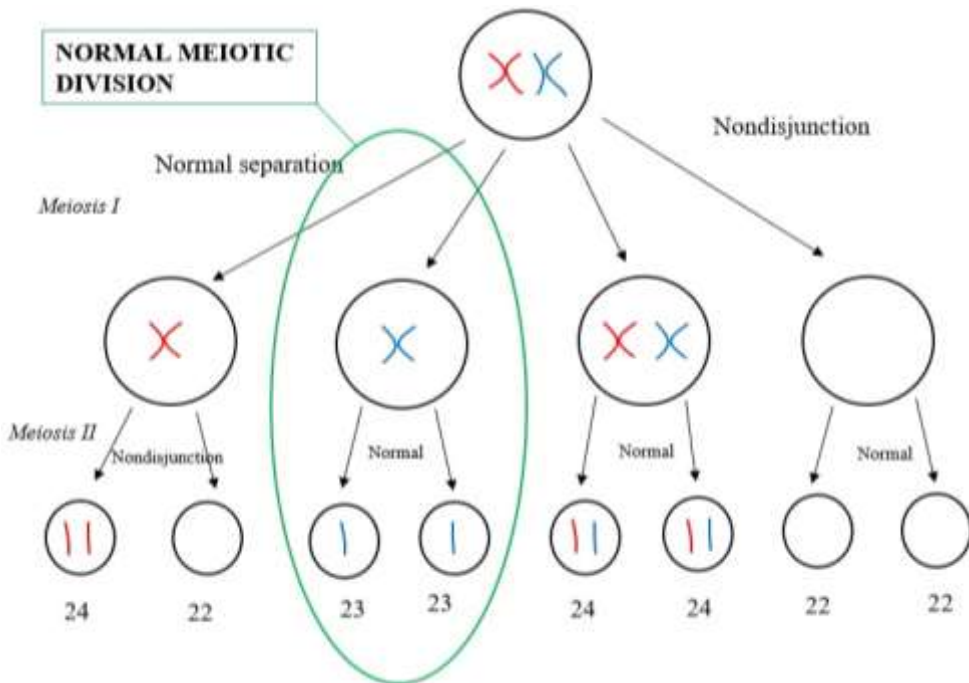


Figure 14. Chromosome nondisjunction during meiosis. Meiosis is cell division in gametes (egg and sperm cells). It consists of two cell divisions, vs. one cell division in mitosis (somatic cells). For simplicity, this figure shows one chromosome pair. (Human cells contain 23 chromosome pairs.) In meiosis I, the chromosome pair segregates into two separate cells. In meiosis II, the chromosome splits at the centromere, halving the genetic material. The process of meiosis II is similar to mitosis. The cells circled in green resulted from correct cell divisions. The remaining cells experienced a nondisjunction event in either meiosis I or meiosis II. Nondisjunction produces cells with too much or too little genetic material, which are almost always incompatible with life. However, excess genetic material can be compatible with life if the chromosome is very small, such as chromosome 21. An extra chromosome 21 is known as trisomy 21, or Down syndrome.

5. NONSYNDROMIC HEARING LOSS

Nonsyndromic hearing loss refers to hearing loss occurring in isolation, in the absence of other clinical features. In this context, we are referring to nonsyndromic hearing losses with genetic etiologies. However, the term “nonsyndromic hearing loss” may be used in cases of isolated hearing loss due to other etiologies or when the etiology is unknown. Bear in mind that many cases of nonsyndromic hearing loss of unknown etiology will in fact have a genetic etiology or a genetic contributor.

Approximately 70% of genetic hearing loss cases are nonsyndromic [79]. Of these genetic nonsyndromic cases, 75 to 80% show an autosomal recessive inheritance pattern, 20% show an autosomal dominant inheritance pattern, and 1 to 2% show an X-linked or mitochondrial inheritance pattern [79]. More than 100 genes have been identified as causative for nonsyndromic hearing loss. For the most up-to-date data, visit the Hereditary Hearing Loss Homepage [9].

5.1. Nonsyndromic Hearing Loss: Autosomal Recessive Inheritance

5.1.1. *Connexin 26 Hearing Loss Is Caused by the GJB2 Gene*

The most common cause of all forms of genetic nonsyndromic hearing loss is the *GJB2* gene, commonly known as connexin 26 [80]. You may also see it referred to as *DFNB1*, its locus name. Connexins are proteins that play supporting roles in the cochlea, and are thought to be important for the recycling of potassium ions in the cochlea [81]. Mutations in the *GJB2* gene are responsible for about half of all cases of autosomal recessive nonsyndromic hearing loss [80]. More than 100 mutations have been reported in this gene [82]. By far, the most common mutation is the 35delG mutation, accounting for about 70% of cases [83]. The 35delG mutation is found in populations all over the world, but it is most common in Caucasian populations, particularly those of northern European or Mediterranean descent [79, 84]. Likewise, this population has the highest carrier rate for the 35delG mutation. The carrier rate refers to the proportion of individuals in a given population who are carriers for a genetic trait or disorder. It generally is used to describe autosomal recessive conditions because carriers of an autosomal recessive condition will not be affected. As previously discussed in section 3.2, a carrier of an autosomal recessive disorder will not exhibit the disorder themselves because they only have one copy of the mutation. Their other gene copy, or allele, is normal, and thus protein function from this gene copy is normal. When a carrier passes on genes to their offspring, each child may get the normal copy or the affected copy, the 35delG mutation in this case. In populations where the carrier rate is high, there is a greater likelihood that two individuals who are carriers for the same disorder will mate. For the 35delG mutation, carrier rates are 2 to 3% for Caucasians, 4 to 5% for Ashkenazi Jewish, and 1% for Japanese [79, 84].

Connexin 26 hearing loss shows a great deal of clinical variability, likely a reflection of the many different mutations and populations in which it is found [80, 85]. As in most forms of autosomal recessive hearing loss, the hearing loss in connexin 26 tends to have an early onset. Hearing loss is usually present in early childhood and may be congenital. In many cases, the hearing loss remains stable, but some cases show a progressive worsening of hearing loss. The type of hearing loss is sensorineural, but the degree is variable. Individuals with connexin 26 can have anywhere from mild to profound hearing loss [85]. The degree of hearing loss can even vary between members of the same family. Both ears are usually affected to the same degree. Though far less common, autosomal dominant mutations in connexin 26 also exist.

5.1.2. *Other Genes*

There are too many genes associated with hearing loss to discuss here. What follows is a brief description of the next seven most common causative genes in autosomal recessive hearing loss. The reader is encouraged to further investigate any genes of interest on OMIM [43]. An exhaustive list can be accessed on the Hereditary Hearing Loss Homepage [9].

5.1.2.1. *SLC26A4*

SLC26A4 codes for pendrin. This is the same gene that causes Pendred syndrome, discussed in section 4.2.1, and thus, hearing loss configuration shows similarities to Pendred syndrome. Different mutations in this gene cause nonsyndromic hearing loss. Onset of

hearing loss is prelingual, frequently congenital. Typical audiometric configuration is moderate to profound sensorineural hearing loss, affecting anywhere from high frequencies to all frequencies. Hearing loss may be fluctuating or progressive. As observed in occurrences of Pendred syndrome, most patients have an enlarged vestibular aqueduct. Mondini defects may be present in some patients [57, 58].

5.1.2.2. *MYO15A*

MYO15A codes for myosin 15A, one of the myosins, a group of motor proteins of many functions, some of which are important for the structure of stereocilia. Onset of hearing loss is prelingual, usually congenital. Typical audiometric configuration is severe to profound sensorineural hearing loss with all frequencies affected [86-88].

5.1.2.3. *OTOF*

The *OTOF* gene codes for otoferlin, a protein thought to be involved in vesicle membrane fusion. Onset of hearing loss is prelingual. This is the most common genetic cause of auditory neuropathy [89].

5.1.2.4. *CDH23*

CDH23, also known as cadherin 23, is another protein expressed in the stereocilia of hair cells [90, 91]. Onset of hearing loss is prelingual, and configuration is severe to profound sensorineural hearing loss. All frequencies are typically affected, but hearing loss may be seen in the high frequencies first [92]. Mutations in the *CDH23* gene are also associated with Usher syndrome type 1D [90].

5.1.2.5. *TMC1*

The *TMC1* gene codes for transmembrane channel-like protein 1. The exact function of this gene is unknown, but it is required for normal function of cochlear hair cells. Autosomal recessive and autosomal dominant mutations have been reported. Hearing loss is usually congenital profound sensorineural with an autosomal recessive mutation, or rapidly progressive severe to profound sensorineural with an autosomal dominant mutation [93-95].

5.1.2.6. *TMPRSS3*

TMPRSS3 codes for transmembrane protease serine 3, a protein whose function is unknown. Hearing loss can be congenital profound or postlingual progressive, often with a ski slope audiogram that eventually progresses to a flat loss [96, 97].

5.1.2.7. *TECTA*

TECTA codes for alpha tectorin, a major structural component of the tectorial membrane. Mutations in this gene are a common cause of mid-frequency hearing loss, exhibiting “notch” or “cookie-bite” audiograms. When inherited recessively, onset is either prelingual or postlingual during childhood or adolescence. (Autosomal dominant mutations are associated with a later age of onset.) Sensorineural hearing loss severity is moderate to profound, often with mid frequencies most affected, and may be progressive [98]. Mutations in this gene have been suggested to be associated with Jacobsen syndrome, a rare disorder characterized by developmental delays and abnormal blood clotting [99].

5.2. Nonsyndromic Hearing Loss: Autosomal Dominant inheritance

Genes associated with autosomal dominant nonsyndromic hearing loss are responsible for a minority, though significant portion of cases. Again, there are too many genes for an exhaustive review. A brief description of the most common causative genes in autosomal dominant hearing loss follows.

5.2.1. *WFS1*

WFS1 codes for wolframin, a protein involved in ion homeostasis. Onset of hearing loss may be prelingual or postlingual in childhood or adolescence. It is characterized by a low-frequency sensorineural hearing loss. Frequencies up to 2 kHz are likely to be affected, but severity usually falls short of profound [100]. Tinnitus is a frequent complaint. Mutations in this gene also cause Wolfram syndrome. Wolfram syndrome is extremely rare and affects many systems. Deafness, progressive vision loss, diabetes mellitus, and diabetes insipidus are characteristic features [101].

5.2.2. *KCNQ4*

KCNQ4, also known as potassium voltage-gated channel, is another protein involved in ion homeostasis. Onset of hearing loss is postlingual, commonly in childhood to young adulthood. Hearing loss is sensorineural, with high frequencies affected first and mid to low frequencies affected later [102, 103]. Severity usually presents as mild to moderate and later progresses to profound. Around 25 to 35% of patients have an increased vestibulo-ocular reflex [104].

5.2.3. *COCH*

The *COCH* gene codes for cochlin, an extracellular matrix protein. Hearing loss tends to present in adulthood, and is progressive sensorineural, with high frequencies most affected. Aside from the hearing loss configuration, clinical presentation often closely mimics Meniere's disease. Vertigo, tinnitus, and aural fullness are all common complaints. Oculomotor disturbances are also common [105, 106].

5.2.4. *GJB2*

GJB2 codes for connexin 26, as previously discussed in section 5.1.1. This is the most common gene associated with autosomal recessive nonsyndromic hearing loss, but there are also mutations in this gene that cause autosomal dominant hearing loss. Onset of hearing loss may be later than the autosomal recessive variety, but often is prelingual or childhood-onset. Sensorineural hearing loss frequently begins in the high frequencies and progresses to affect the mid frequencies. In about half of cases, skin disorders are present, characterized by hyperkeratotic skin lesions [107]. The *GJB6* gene, also known as connexin 30, is a less common autosomal dominant hearing loss gene which shows a similar presentation, absent the skin lesions.

5.3. Nonsyndromic Hearing Loss: X-Linked Inheritance

X-linked nonsyndromic hearing loss is rare. The best-known gene in X-linked nonsyndromic hearing loss is *POU3F4*. Onset is prelingual. Mutations in this gene lead to defects in the bony labyrinth. Stapes fixation is common, and thus hearing loss may be mixed or sensorineural [108]. The stapes fixation may be addressed surgically, but there is a risk of perilymphatic gusher during surgery. Perilymphatic gusher is a phenomenon whereby a rush of perilymph exits the cochlea during stapedotomy or stapedectomy [109]. Because of this risk it is very helpful for the surgeon to know in advance of *POU3F4* involvement, both for risk assessment and surgery strategy. As with other X-linked genes, most affected individuals are male.

5.4. Nonsyndromic Hearing Loss: Mitochondrial Inheritance

Hearing loss due to a mutation in a mitochondrial gene is rare, but they are noteworthy because of their role in ototoxic-induced hearing loss. Recall from section 3.4 that mitochondria have their own genome separate from the nuclear genome. The mitochondrial genome consists of only 37 genes. A1555G is a mitochondrial mutation in the 12S rRNA gene, and it is the most common mitochondrial mutation causing hearing loss [110]. Since this is a mitochondrial mutation, it is inherited from the mother. The carrier rate is highest in Asian populations [110-112]. About half of individuals with this mutation develop hearing loss, usually after age 30. However, hearing loss can occur much earlier if an individual with this mutation receives aminoglycoside antibiotics (amikacin, dihydro-streptomycin, gentamicin, kanamycin, neomycin, streptomycin, tobramycin). Though rarely encountered in the United States, deafness associated with this mutation is much more common in China. The combination of high carrier rates and overuse of antibiotics has increased the rates of deafness due to this mutation in China [111, 112]. Use of aminoglycoside antibiotics over non-aminoglycosides should be carefully considered and utilized only when the benefits outweigh the risks.

The type of hearing loss is sensorineural. The degree of hearing loss can vary from mild to profound, but is likely to be severe to profound if the individual is exposed to aminoglycoside antibiotics. Hearing loss can occur a few days or weeks after aminoglycoside administration, even after a single dose [110]. As mitochondria are thought to have been independent single-celled organisms billions of years ago, their cellular structure and genome are similar to that of bacteria. Aminoglycoside antibiotics work by binding to the bacterial ribosome and disrupting protein function. The A1555G mutation essentially makes the ribosome more similar to a bacterial ribosome [113].

6. TECHNOLOGIES IN GENETIC TESTING

6.1. Cytogenetics

Cytogenetics is the branch of genetics that evaluates chromosome structure and function. This can be viewed as assessing the genome at the cellular level (cyto=cell). Visualizing

chromosomes means we are “zoomed out” relative to molecular testing. The cellular view corresponds to a bird’s-eye view: we are getting a large-scale view, but we cannot see small details. Cytogenetic testing is useful for detecting changes in chromosome number and structure: too many chromosomes, missing chromosomes, and large structural aberrations. It will not detect small rearrangements or mutations such as point mutations (substitution of one base of DNA for another). These rearrangements are simply too small for us to see from our zoomed-out vantage point. The major testing tools in cytogenetics are karyotyping, FISH, and array CGH. An explanation of each follows.

6.1.1. Classical Cytogenetics: Creation of a Karyotype

A karyotype is a preparation of chromosomes from one cell, in which the chromosomes are arranged according to their numerical assignments. Recall from section 2.3 that a human cell is expected to contain 46 chromosomes: 44 autosomes and 2 sex chromosomes. Males and females differ only in their sex chromosome complement. A typical male will have a karyotype of 46,XY and a typical female will have a karyotype of 46,XX. There are several steps necessary to prepare a karyotype. First, cells must be cultured anywhere from 24 hours to 8 to 10 days, depending on sample type and viability. Many sample types require addition of a mitogen, such as PHA (phytohemagglutinin) to stimulate cell division. Direct samples without culturing are sometimes used when results are needed urgently, but this is not utilized frequently, as morphology tends to be poor. Many different tissue types can be used for cytogenetic testing, including peripheral blood, bone marrow, amniotic fluid, chorionic villus sampling, skin biopsy, tumors, and products of conception (abortus material, typically from spontaneous abortions), among others. These tissue types represent the diverse patients who undergo cytogenetic testing. Diagnostic usefulness encompasses disparate needs, such as prenatal, cancer, developmental delay, and infertility. Buccal cells, epithelial cells collected through saliva or cheek swabs, cannot be used for cytogenetic testing because they do not grow sufficiently in culture. They can, however, be used in DNA testing (Sections 6.2 and 6.3).

After cells are cultured to increase cell growth and cell division, samples are harvested to obtain chromosome spreads which can be used in a karyotype. The purpose of the harvest procedure is to accumulate cells in metaphase of mitosis. This is the phase of mitosis where the chromosomes reach maximal condensation and are most readily analyzed. The harvest procedure requires a series of steps and takes several hours:

1. Incubation with colchicine: Colchicine poisons the mitotic spindle, which is necessary for chromosomes to split into two daughter cells and complete mitosis. Colchicine allows for a greater number of cells in culture to accumulate in metaphase. Without colchicine, very few cells would be in metaphase, making analysis difficult to impossible.
2. Incubation in a hypotonic solution: Cells are collected by centrifugation and a hypotonic solution is added. This solution will be at a concentration that is slightly hypotonic to the cells in culture. Through the property of osmosis, water will move from a less concentrated solution to a more concentrated solution. Water will therefore move from the hypotonic solution and into the cells. The purpose of this solution is to swell the cells just enough to allow the chromosomes to spread, but not

enough so that the cells burst. Spreading the chromosomes aids greatly in analysis. Commonly used hypotonic solutions are potassium chloride and sodium citrate.

3. **Addition of a fixative:** After the appropriate incubation time in hypotonic solution, a fixative is added, typically a 3:1 solution of methanol:acetic acid. This fixes, or preserves the cells, and removes excess water and cellular debris. At this point the cells are no longer alive. Several fixative changes may be necessary.
4. **Slide preparation:** Cells are dropped onto slides and aged overnight on a hot plate.
5. **Slide staining:** Slides are treated with trypsin, an enzyme that digests proteins bound to DNA and allows the chromosomes to take up stain in a characteristic banding pattern. Slides are then stained with a deep stain, such as Giemsa or Wright stain.
6. **Chromosome analysis and karyotyping:** Chromosomes are analyzed under a light microscope at 100x magnification. An imaging system attached to the microscope is used to photograph desired cells, which are then karyotyped on a computer. The end result is a completed karyotype (Figure 2).

For a more detailed review, see Howe et al. [114].

During chromosome analysis, the technologist will find a metaphase cell under the microscope suitable for analysis. The chromosomes are counted, and then evaluated one chromosome at a time to ensure all expected bands are present. For a typical case, 20 cells are analyzed. This may be increased to 50 or 100 cells if mosaicism is suspected or discovered. Mosaicism means that there is more than one chromosome complement in an individual. This is not common, but does sometimes occur due to a postzygotic nondisjunction event (see section 4.5).

Aside from chromosome number, cytogenetic analysis also seeks to discover structural aberrations. There are 4 major types of chromosome aberrations:

1. *Deletion:* A section of a chromosome is missing.
2. *Duplication:* A section of a chromosome is repeated.
3. *Inversion:* A section of a chromosome is flipped, as if a piece was removed, turned around, and then inserted back into the chromosome. With an inversion, no material is missing or gained, just rearranged. In most cases this is benign, such that the individual carrying a chromosomal inversion does not know unless they happen to get a karyotype. In rare cases an inversion can cause problems if the chromosome happens to be cut within a gene. A person carrying an inversion is also at increased risk of having a child with a deletion or duplication in the breakpoint regions.
4. *Translocation:* Sections of two or more chromosomes are exchanged with one another. Translocations can be balanced or unbalanced. When balanced, there is rarely a consequence to the individual carrying a translocation. However, like inversions, there is a risk to offspring because a child can inherit an unbalanced form. When unbalanced, there will be extra material from one chromosome and missing material from another chromosome. This is essentially like having both a deletion and a duplication.

How deleterious these chromosomal aberrations are depends on several factors, and are not always predictable. In general, larger deletions and duplications are more deleterious than smaller ones, but very small deletions and duplications can have enormous consequences as

well. The number of genes affected, redundancy of those genes, and influence of modifier genes will all affect the patient's clinical presentation. Chromosome analysis is useful for identifying these aberrations, but even the smallest deletions and duplications can only be visualized microscopically if they involve hundreds of thousands of base pairs of DNA. This is a major limitation of karyotyping. The next two techniques allow us to zoom in a bit further and identify smaller aberrations.

6.1.2. FISH: A Molecular Cytogenetic Technique

The smallest of chromosomal deletions that are visible microscopically are about 200 to 300 kilobases of DNA (1 kilobase=1,000 bases), and even that size is difficult unless chromosome length, spreading, and banding are optimal. These small deletions, also known as microdeletions, can be visualized by a technique known as FISH (fluorescence *in situ* hybridization). FISH is considered a molecular cytogenetic technique because it utilizes similar principles to that employed in polymerase chain reaction and other molecular techniques. The process is relatively simple. A slide is prepared after chromosome harvest, but the slide is not aged or stained. The slide is heated at high temperature to denature the

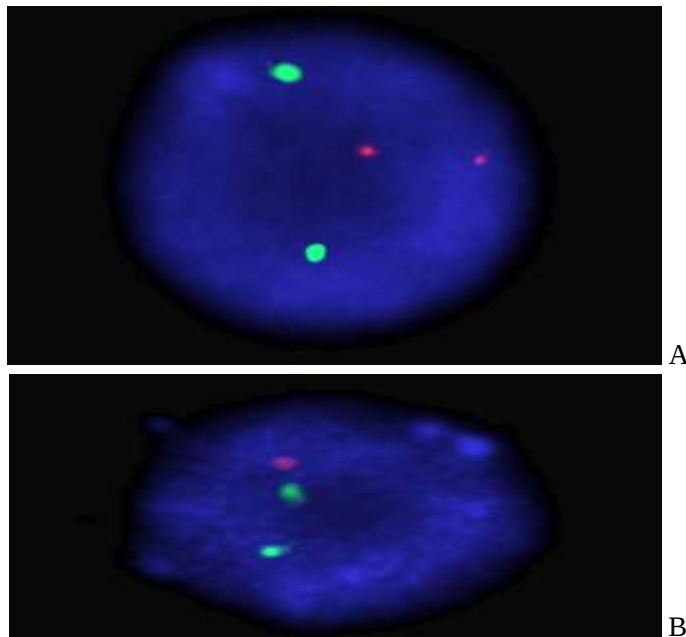


Figure 15. Fluorescence *in situ* hybridization (FISH). Pictures of human lymphocytes from two patients stained with FISH probes. These cells were probed for the *RB1* gene, a tumor suppressor gene located on chromosome 13, tagged with a red fluorescent probe. Deletion of *RB1* is associated with retinoblastoma, an aggressive ocular cancer. A centromere probe on chromosome 10, tagged with a green fluorescent probe, is used as a control. Since two copies of each *RB1* and chromosome 10 are expected, the anticipated result is two red signals and two green signals. The cell in A is normal, with two copies of each signal. The cell in B only has one red signal due to deletion of one copy of the *RB1* gene. This patient would be expected to develop retinoblastoma. FISH pictures are courtesy of the laboratory of Dr. Fern Tsien, Louisiana University Health Sciences Center Department of Genetics, used with permission.

DNA into two separate strands. A FISH probe is added to the slide and incubated. This probe consists of two components: a stretch of DNA (~100-300 kilobases) complementary in sequence to the desired area attached to a fluorophore. During incubation, the denatured DNA will renature with the FISH probe. The slide is visualized under a fluorescent microscope in the dark. The fluorophore present will excite and fluoresce when exposed to the appropriate wavelength of light. Fluorophores are available in a variety of colors, with red, green, and aqua being the most commonly used.

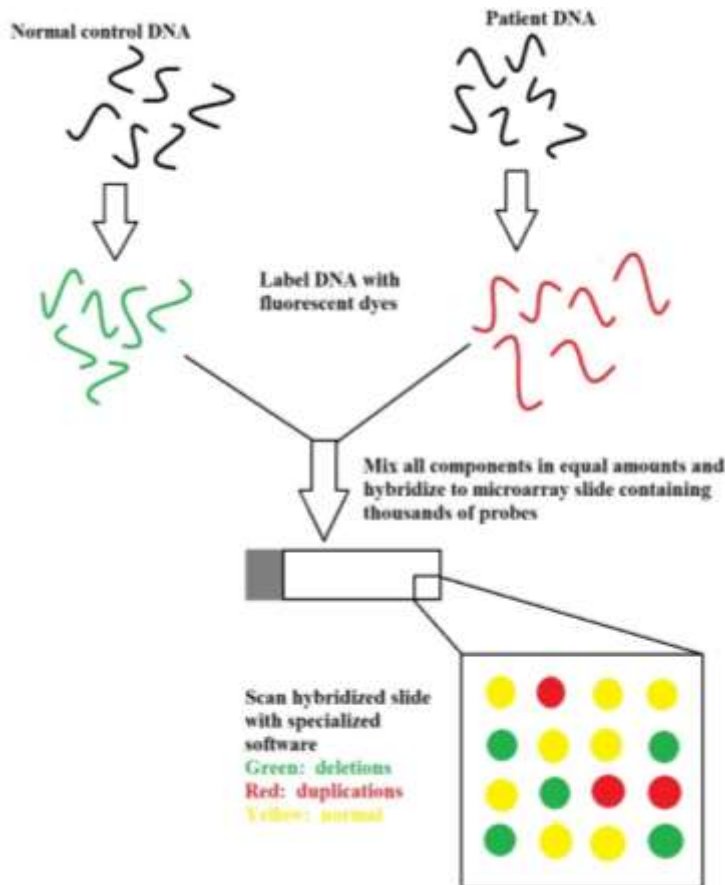


Figure 16. Array CGH. Array CGH (comparative genomic hybridization) is illustrated here. Thousands of probes are attached to a slide. DNA from the patient is mixed with normal control DNA and labeled with fluorescent dyes. After hybridization, the slide is scanned and analyzed with specialized software. The red and green dyes will appear yellow when combined in equal amounts. Areas of gene deletions will appear green (patient DNA is missing), while areas of gene duplications will appear red (patient DNA is in excess of control DNA). Balanced rearrangements are undetectable with this method.

FISH has a few advantages over the karyotype. Its greatest advantage is in identifying microdeletions or microduplications that are too small to detect with standard cytogenetics. For most FISH probes, interphase cells can be analyzed, yielding many more cells to work with. Preparations by FISH also work fairly well on uncultured cells and the test has a fast turnaround time, making FISH more amenable to “stat” testing. A major drawback with FISH is that each probe used is only testing a very specific chromosomal region. In other words,

you need to know what you are looking for. This usually means the physician must suspect the correct syndrome and request FISH testing for that syndrome. Figure 15 shows a picture of a cell tested with a FISH probe.

6.1.3. Array CGH: Molecular Cytogenetics of the Entire Genome

In the last decade, the karyotype has been largely replaced with array CGH (comparative genomic hybridization). Array CGH is a technique that combines important components of karyotyping and FISH. A simplified view of array CGH is demonstrated in Figure 16. A microarray is a slide containing thousands of probes covering the entire human genome. DNA from the patient's sample is isolated and labeled with a fluorescent dye (red in this example). DNA from a known genetically normal individual of the same gender is labeled with a different fluorescent dye (green). The samples are mixed together and applied to the microarray, where they are incubated and allowed to hybridize to the thousands of probes on the array. The microarray slide is scanned by a computer with specialized software. Deletions and duplications are identified based on the color of every probe in the array. If there is no gain or loss of material, the color will appear yellow due to the mixing of the red and green probes. A loss of material (deletion) will appear green and a gain of material (duplication) will appear red. When a deletion or duplication is identified, it is confirmed by FISH testing.

Array CGH has many of the advantages of FISH probes, but the whole genome is evaluated much as in the karyotype. With this technique, it is not necessary to know exactly what you are looking for because all of the probes are already included. There is a major limitation of array CGH compared to karyotyping. Array CGH only shows gains and losses of genetic material. It will not show balanced rearrangements. Therefore, an individual carrying a balanced translocation or inversion will not be detected by array CGH. It is for this reason that the karyotype will not be completely supplanted by array CGH.

6.2. Polymerase Chain Reaction and Gel Electrophoresis

The polymerase chain reaction (better known as PCR) is perhaps the most significant advancement in molecular biology. Developed by Kary Mullis in 1983, PCR has revolutionized molecular genetics, being widely used in medicine, forensics, and scientific research. PCR is a method of amplifying DNA. This allows one to analyze a particular region of DNA when there are very small quantities present. The amplification of DNA is analogous to photocopying a page from a large book, as if that page was torn out and photocopied millions of times. PCR reactions are generally 30 to 100 μ l in volume, but can be as low as 10 μ l. Small quantities of the following are transferred by micropipet into PCR tubes:

1. *DNA template*: DNA from the sample to be tested
2. *Primers*: 2 short DNA sequences (~15-25 bases) complementary to the region/gene being tested
3. *dNTPs (deoxynucleotide triphosphates)*: nucleotide bases A, G, C, T of DNA
4. *DNA polymerase*: enzyme that makes new DNA through addition of bases
5. *Magnesium ions*: works as a cofactor for DNA polymerase
6. *Buffer solution*: for stability of DNA polymerase.

The prepared PCR reactions are placed in a thermal cycler. A thermal cycler is a machine capable of rapidly changing temperature. This is the key to the PCR process, the bulk of which involves repeated cycles of short incubations at three different temperatures. First, the samples are heated to a high temperature around 95°C to denature the DNA sample. Once denatured, the temperature is quickly lowered to around 60°C, a temperature ideal for annealing. Annealing is where the primers bind to their complementary sequence of DNA. The temperature is then raised to 72°C for elongation, a temperature at which the polymerase enzyme works optimally. The polymerase adds bases from the dNTP mix. The polymerase used in PCR is *Taq* polymerase, obtained from the bacteria *Thermus aquaticus*. This species of bacteria thrives in very hot environments, and thus its polymerase is stable at very high temperatures. At the end of each PCR cycle, there are twice as many DNA fragments of the desired region. After 30 to 40 cycles of PCR, you are left with millions of copies of this DNA fragment, even if you started with just one. Figure 17 shows a simplified schematic diagram of this process.

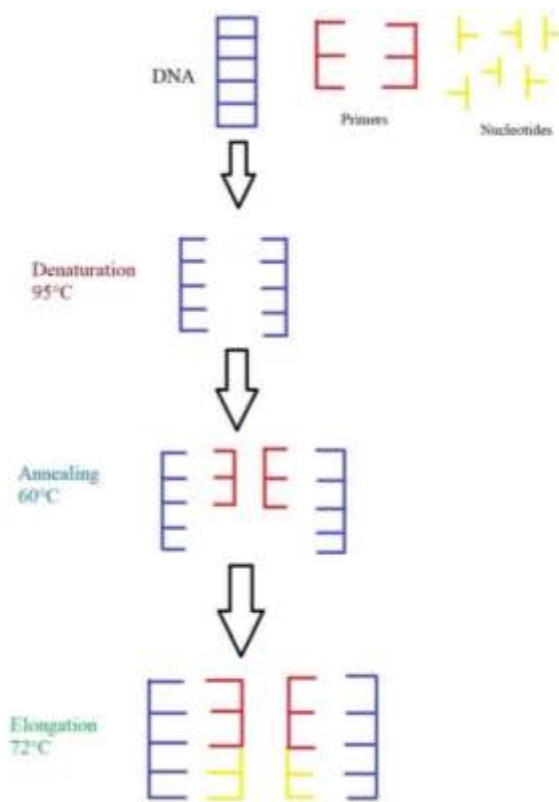


Figure 17. Polymerase Chain Reaction (PCR). One cycle of PCR is illustrated here. The DNA sample being tested is mixed with nucleotides and primers which will form the building blocks necessary to produce more DNA copies of a desired region of DNA. One cycle consists of denaturation, annealing, and elongation. The DNA is denatured into two strands by heating at a high temperature. The temperature is lowered to allow the primers to anneal to their complementary strands. The temperature is raised back up to the optimal working temperature of DNA polymerase, which will add nucleotides to build a new DNA strand. At the end of the PCR cycle, you are left with double the amount of DNA from the start of the cycle. A typical PCR run will include 30 to 40 cycles, resulting in millions of DNA copies of the desired gene or region. The PCR products can then be visualized via gel electrophoresis.

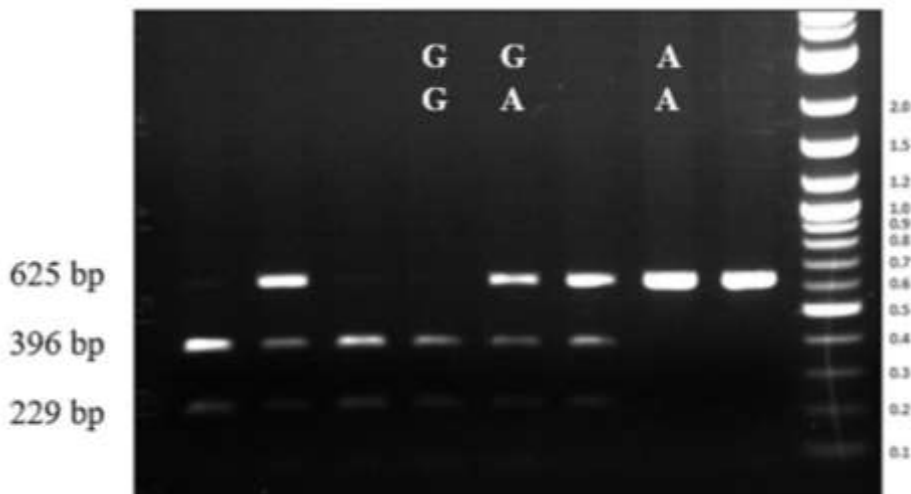


Figure 18. Gel electrophoresis. Agarose gel electrophoresis after PCR for the G216A mutation in the *USH1C* gene. The normal genotype at this site is GG. A substitution of G to A results in Usher syndrome if two copies are present (Usher syndrome is autosomal recessive). PCR products are separated by size, with smaller fragments moving faster through the gel. Fragment sizes in base pairs (bp) are listed on the left of the picture. The far right lane contains a DNA ladder of known fragment sizes. Three patient samples are labeled: GG (normal), GA (carrier for Usher syndrome), and AA (Usher syndrome). Gel picture courtesy of the laboratory of Dr. Fern Tsien, Louisiana University Health Sciences Center Department of Genetics, used with permission.

The PCR products can be loaded on a gel and run through gel electrophoresis to visualize the results. The main types of gels used are agarose and acrylamide. The gels are of a somewhat porous material so the DNA can move through the gel. An electric current is run through the gel after the samples are loaded. Since DNA has a negative charge, the samples are loaded at the negative pole and migrate toward the positive pole once the electric current is introduced. The gel acts as a sieve, allowing smaller DNA fragments to migrate through the gel at a faster rate than the larger fragments. The end result is a separation of DNA fragments based on size. A chemical dye such as ethidium bromide is added to the gel to allow for visualization. Ethidium bromide binds to DNA and fluoresces under ultraviolet light. An example of an agarose gel electrophoresis following PCR is shown in Figure 18.

PCR is specific and, if designed properly, can identify single base-pair changes. It is relatively cheap to run and has a great deal of versatility. There are many downstream applications for PCR which are too complex to describe here. It can be regarded as a “zoomed-in” procedure. We are evaluating specifically what we designed our primers for, not the entire genome. We will therefore not identify a disorder in a different gene.

6.3. DNA Sequencing

DNA sequencing determines the exact base sequence of a strand of DNA. This can be a targeted sequencing or a whole genome sequencing. Targeted sequencing tests a specific region, usually a particular gene or set of genes. Whole genome sequencing tests the entire genome of an individual. The latter is obviously far more complex, time-consuming, and

expensive. Major methods of DNA sequencing employed today are Sanger sequencing and next generation sequencing. Sanger sequencing was one of the original DNA sequencing techniques developed, and has largely been replaced by next generation sequencing techniques in the last decade. However, Sanger sequencing is still used, mostly for targeted sequencing. The process of DNA sequencing will not be discussed here. The interested reader is encouraged to explore this topic independently.

6.3.1. Genome Sequencing

In 1990, the Human Genome Project was launched as an international collaborative effort to sequence the entire human genome. It took years to complete, but finished ahead of schedule in 2003. Today's next generation sequencing techniques have managed to drastically cut down the testing time. In recent years, whole genome sequencing is gaining widespread use in clinical testing. It has become cheaper and faster, and has allowed for a diagnosis in patients who previously tested normal by other methods. However, it is still expensive relative to other methods, and turnaround time by a clinical laboratory takes several weeks or months for testing and analysis of results. Exome sequencing is a frequently-used alternative that cuts down on the amount of DNA to analyze.

6.3.2. Exome Sequencing

Over 98% of the human genome does not code for proteins. When performing clinical testing on a patient suspected of a genetic disorder, sequencing analysis can be greatly reduced by focusing on these coding regions. Recall from section 2.1 that genes are transcribed into mRNA. The initial mRNA is a complement to the DNA gene from which it was transcribed. Human genes contain exons and introns. Exons are the sequences responsible for coding for the resultant protein, while introns contain regulatory elements and non-coding sequences. The evolutionary purpose of introns is unclear. As the introns are unnecessary for coding of the protein, they are removed from the mature mRNA molecule.

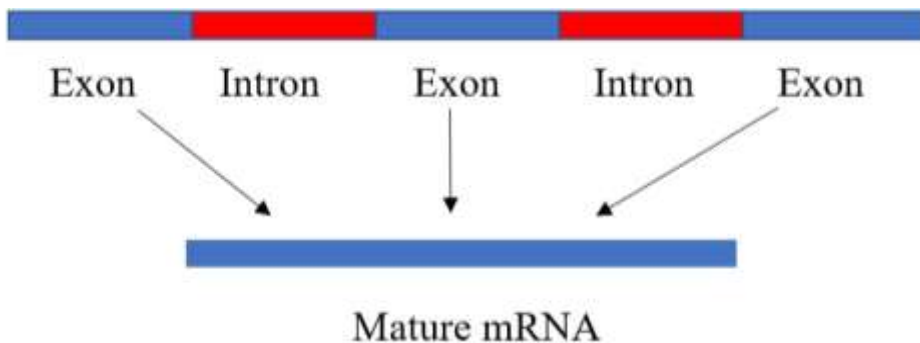


Figure 19. Exons and introns. The DNA sequence of a gene includes exons (coding regions) and introns (noncoding regions). Once a DNA sequence is transcribed into mRNA, the introns are removed and the exons are joined together during a process known as RNA splicing. Exome sequencing analyzes only the exons. Most disease-causing mutations will be found in the exons, and thus exome sequencing is a quicker and more cost-effective method for identifying mutations. However, deleterious mutations do occur on occasion in the introns if they lead to aberrant splicing. Genomic sequencing analyzes both exons and introns.

This is illustrated in Figure 19. The exons now can be sequenced without the baggage of the introns. This process is exome sequencing. It has the advantage over whole genome

sequencing of being cheaper and faster while still having the capability of finding most of the same mutations. However, while uncommon, deleterious intronic mutations do exist. An intronic mutation can affect a regulatory element, which can cause the exons to be spliced in an alternative way. This can affect the protein product and cause disease. Exome sequencing will not identify all intronic mutations.

While genome and exome sequencing are not yet mainstream clinical applications for testing patients with nonsyndromic hearing loss, they are being used in research settings. This is leading to identification of more genes associated with hearing loss. As the cost continues to drop these tests may gain traction for diagnosis of genetic hearing loss.

7. MAKING A GENETICS REFERRAL

7.1. When Should a Genetics Referral Be Made?

For most patients who may benefit from genetic testing, a referral from a health care professional is needed, as few patients or families will seek this out themselves. In cases of hearing loss with a genetic etiology, the audiologist is a key player in achieving this diagnosis. Of course, any health care professional can recommend a genetics evaluation, and this is frequently initiated by primary care physicians and specialty physicians. However, in cases of hearing loss, physicians may defer to audiologists to make these calls. On the other hand, audiologists frequently defer to physicians to address genetic testing because the evaluation is viewed as medical in nature. Unfortunately, this results in many patients being missed until other health effects from a syndrome surface or hearing loss recurs in another family member. By this time many of the benefits of genetic testing have been lost. If audiologists want to be viewed as the authority on hearing loss, we must take a leadership role in all aspects of hearing and balance, including genetics of hearing loss. This is particularly applicable to pediatric audiologists, whose patients and families have the most to gain from a genetics evaluation. Deferring the referral to physicians, many of whom know far less about both hearing loss and genetics than audiologists, we are missing an opportunity to assert our expertise. This ultimately results in a disservice to our patients. This does not mean that every audiologist must be an expert in genetics or have an in-depth understanding of genes involved in hearing loss or genetic testing methods. It does mean, however, that every audiologist should understand when to make a genetics referral, how to talk to patients and families about genetic testing, and what the ramifications are of various test results. (For clarification, the use of the term *referral* in this chapter is roughly equivalent to *recommendation*. It is not used in association with insurance coverage, which varies by plan and may require a physician order. Insurance coverage is inconsistent for genetic testing.)

So when should an audiologist make a referral for a genetics evaluation? Put simply, a referral can be made in any case of permanent hearing loss with an unknown etiology if the patient or family desires. This will start with a discussion with the patient or the patient's family (in pediatric cases) about the possibility of a genetic etiology. This should be done in a sensitive manner, and may begin by asking if they have ever considered genetic testing or a genetic etiology. This will help assess whether anyone else has suggested a genetic etiology and what the family thinks about it. This can begin the conversation and allow the audiologist

to discuss possible benefits of receiving a genetics evaluation. It should be noted that genetic testing is not for everyone, and it will not benefit everyone. Some patients and families will elect to decline a genetics referral for a variety of reasons. This is their choice and that choice should be respected. Patients and families should never feel pressured to undergo genetic testing or shamed for declining. Our role as audiologists is to ensure patients are made aware of the possibility of a genetic etiology and have the opportunity to seek that out should they desire. Patients should also be made aware that an evaluation with a geneticist and/or genetic counselor does not mean they will or must receive genetic testing. Part of this evaluation should include assessment for emotional readiness for genetic testing, which may conclude with declination of testing.

There are several characteristics which, when present, increase the likelihood of a genetic etiology, and should therefore be considered when discussing a genetics referral. Perhaps the strongest is a family history of hearing loss, particularly a family history of congenital or early-onset hearing loss. An increase in the number of relatives and closeness of relationship with the patient will each increase the likelihood that the cause is genetic. First-degree relatives (children, parents, and siblings) carry the most weight because these relatives share, on average, half of their DNA with one another (or all of their DNA, in the case of monozygotic twins). Second-degree relatives (aunts, uncles, grandparents) share, on average, a quarter of their DNA, and are also significant in the family history. Third-degree relatives (such as first cousins) should not be dismissed, especially if there are two or more affected family members. Third-degree relatives carry greater weight in families with consanguinity, meaning there is a mating between blood relatives. In families with consanguinity there is an increased risk of having offspring with an autosomal recessive disorder. This may include deafness/hearing loss. While a family history of hearing loss increases the chances of a genetic etiology, the absence of a family history does not exclude a genetic cause. Recall that over 90% of children born with permanent hearing loss are born to hearing parents, and in many cases there is no known family history on either side. Genetics referrals should not be dismissed because there is no family history. The Joint Committee on Infant Hearing position statement recommends referral for a genetics evaluation for children born with permanent hearing loss [115].

Another characteristic increasing the likelihood of a genetic etiology is the presence of other clinical features. These features may be readily apparent, such as dysmorphologies or distinct facial features, or they may be less conspicuous. Hearing loss accompanied by cardiac problems, kidney problems, thyroid problems, vision loss, fainting spells, or skin lesions should be heavily suspected as being genetic. In addition, hearing loss (especially deafness) occurring after administration of a normal dose of aminoglycoside antibiotics may be due to a genetic mutation. If common hearing loss-associated infections have been ruled out as the cause, odds are increased that the cause is genetic. Finally, unusual audiometric configurations (such as “cookie-bite” audiograms or low-frequency sensorineural hearing loss) often have a genetic cause, especially if there is a family history.

Most genetics referrals are made for pediatric patients or cases where a syndrome is suspected. These are the patients and families who have the most to gain from genetic testing. In cases of adult-onset nonsyndromic hearing loss, a referral may or may not be made. For many of these patients the costs may outweigh the benefits. Nonetheless, a discussion could be held with the patient, and a referral considered in the presence of a strong family history if the patient desires. In the absence of a strong family history in a patient with adult-onset

hearing loss, genetic testing is unlikely to yield useful information. Genetic testing can be laborious, expensive, and emotionally draining, and it is not always fruitful. Benefits, impacts, and limitations of genetic testing must all be considered with each patient. This will be the responsibility of clinical geneticists and genetic counselors.

7.2. Benefits of Genetic Testing

There are several potential benefits of genetic testing for patients with hearing loss. In cases of syndromic hearing loss, the diagnosis can direct clinical evaluation and treatment for associated disorders. For example, a diagnosis of Jervell and Lange-Nielsen syndrome will lead to close monitoring for cardiac issues. Without this diagnosis, the patient would not know to seek treatment until experiencing an adverse event. Likewise, a diagnosis of Usher syndrome received before the onset of vision loss would allow for the patient to undergo ophthalmologic evaluation and the patient's family to prepare for the future, such as early teaching of Braille. Patients have a better opportunity to take care of themselves if they are aware of potential health consequences associated with their syndrome.

Another major benefit of genetic testing is an allowance of estimation of recurrence risks for patients and/or their families. For some families this will be very important and may be the driving motivation for obtaining genetic testing. For other families, this will not be important at all. Discussions on recurrence risks, handled by the genetics team, should be addressed sensitively. It should not be assumed that all families will want this information, and some may feel offended by the topic. However, there will be families who would like to know the odds of having another affected child, and they may or may not use this information for family-planning purposes.

A genetic diagnosis may affect distant members of the patient's family, should the family opt to share this information. Depending on the family, this may be viewed as a benefit, a drawback, or of no consequence. If other family members are informed of the diagnosis, this may enable them to receive an early diagnosis, thereby optimizing treatment and yielding risk estimates for their offspring. However, distant family members may not welcome this information, and may even be resentful that it is thrust upon them. On the other hand, some families may not want to share their diagnosis with family members, either because they are not close to their family, they want to keep their medical information private, or they are unsure if the information will be welcome. These different scenarios may cause tension amongst family members or feelings of guilt in members of the presenting family.

In some cases there may be no real benefit other than having a diagnosis. For some families it is satisfying to know the reason behind the hearing loss and other features (if present) even if it is of no consequence in family-planning or health monitoring. Some patients or parents find peace of mind in knowing the cause, which can be a benefit in and of itself. The benefits of genetic testing are less clear with adult-onset hearing loss. By adulthood, a syndrome likely would have been identified already, and recurrence risks are usually not important to individuals who may pass on adult-onset hearing loss. Also, by the time someone reaches adulthood there are many other potential causes to consider, lowering the chances of identifying a genetic etiology. Nonetheless, there may be patients where testing may be pursued. Again, genetic testing for these patients is often futile unless there are

several family members affected with a similar presentation (i.e., type, onset, progression, and configuration of hearing loss).

7.3. Impacts of a Positive Genetic Test Result

During the genetics evaluation, the genetic counselor will discuss with the patient and/or patient's family how they may be impacted by the results of the test. This will be taken into consideration before genetic testing is performed. A positive test result can have negative psychological or social effects for the patient and the patient's family. Genes make up who we are, causing a genetic diagnosis to feel deeply personal for some people. As previously discussed, a positive test result can affect other family members who may or may not be prepared to receive this information. For parents, feelings of guilt are common. Tension between parents may ensue, especially if the mutation in question is found to be inherited exclusively from one parent. Parents may be prone to assign blame, even if inadvertently. Some have raised ethical concerns with the genetic testing of children, arguing such testing violates a child's right not to know. There is legitimacy to this argument; genetic testing of minor children should never be taken lightly. These issues should be explored with the genetic counselor when the family is deciding whether or not to pursue genetic testing.

7.4. Limitations of Genetic Testing

Just as there are potential ramifications to patients and their families with a positive test result, families must also face the possibility of a negative test result. Families may complete genetic testing feeling lost and confused if the process does not result in a diagnosis. This outcome is far more common than one might expect when considering the prevalence of genetic hearing loss, and there are a few reasons why this would happen. The most obvious explanation for a negative test result is that the cause of the hearing loss is not genetic. However, one cannot conclude this based on a negative genetic test result unless there is another viable explanation for the etiology, in which case genetic testing probably would never have been initiated. This may be the most common error made by patients and health care providers alike regarding genetic test results. On the contrary, a negative result on a genetic test does not necessarily mean the cause is not genetic. Rather, one can only conclude that a genetic etiology for what the test examined can be ruled out.

Recall that there are over 400 genes associated with syndromic hearing loss and over 100 genes associated with nonsyndromic hearing loss. Consider a patient with nonsyndromic congenital deafness with an extensive family history presents for genetic testing. Based on evaluation of family history of autosomal recessive inheritance and limited insurance coverage for genetic testing, a decision is made to sequence the patient's *GJB2* gene, also known as connexin 26. Because mutations in connexin 26 cause more cases of nonsyndromic hearing loss than any other gene, this approach is reasonable. Testing comes back as negative and this is reported to the family. All that can be concluded from this result is that connexin 26 is not the cause of deafness in this patient (and presumably in this family, although some families have been found to have more than one causative gene). We have no information on the 100+ other genes which were not tested. If a result is still desired, another gene must be

selected for testing, and it is not easy deciding which way to go next. To make this example even more specific, let us imagine that instead of sequencing connexin 26, a molecular test is performed for 35delG, the most common mutation in connexin 26 deafness. The test may be ordered this way because it is even more cost-effective than sequencing of the entire gene, but it will only detect cases caused by the 35delG mutation. In this example, a negative result would not even rule out connexin 26 as the causative gene. Rather, it would only rule out a connexin 26 35delG mutation.

Because testing is expensive and insurance companies will not always cover it, starting with the most likely gene to yield a positive result is a common approach. Over the last decade gene panels for various disorders, including hearing loss have been developed. Hearing loss panels are offered by some testing laboratories, and allow for simultaneous molecular testing of many mutations in several different genes, increasing the likelihood of a positive result in a single test. Sequencing tests will identify more mutations, but the time and costs involved make it prohibitive for many patients, especially in cases of nonsyndromic hearing loss. Fortunately, these comprehensive tests have been getting gradually faster and cheaper, so they may be more accessible for clinical testing in the future. However, even sequencing does not identify the causative gene for all patients. Exome sequencing only sequences the coding regions of genes, which is where most mutations occur. But mutations in introns can disrupt regulatory elements in genes, affecting gene expression. Sequencing the entire genome will include intronic regions, but the large amount of data generated can be difficult to interpret. Thus, sequencing can miss the cause because the gene in question has not been identified to be associated with the disorder being tested. As testing methods improve there will be fewer patients who do not obtain a diagnosis. But in today's world, a negative test result is common for families of hearing loss as well as many genetic disorders.

7.5. Testing Recommendations

The testing panel will be determined by the geneticist. Audiologists can aid the process by communicating pertinent information about the patient's audiological evaluation [116]. This includes type of hearing loss, severity, age of onset, progression, audiometric configuration, family history, and presence of auditory neuropathy or vestibular disturbance. These characteristics can give clues on which gene may be involved. If audiograms are available from affected family members, these may prove to be helpful as well. In cases of nonsyndromic hearing loss, the presenting characteristics may be suggestive of inheritance pattern. Nonsyndromic hearing loss with an autosomal recessive inheritance pattern is more likely to have a prelingual onset, be stable in degree, and affect most or all frequencies. Conversely, nonsyndromic hearing loss with an autosomal dominant inheritance pattern is more likely to have a postlingual onset, be progressive, and affect a subset of frequencies. These are *general* characteristics, and vary by gene, mutation, individual, and family. They will *not* always hold true, but should be considered in conjunction with the inheritance pattern displayed in the family history. Due to the high incidence of congenital and early-onset hearing loss caused by cytomegalovirus (CMV), this infection should be considered when reviewing a patient's medical history. Newborn screening for CMV is being tested in hospitals in the United States, and may be incorporated in the future as part of the newborn hearing screening program [117]. CMV-related hearing loss presentation can appear similar

to genetic hearing loss. A positive CMV test will prevent unnecessary genetic testing. Unfortunately, CMV testing methods lack sensitivity to reliably detect congenital CMV after 3 weeks of age [117]. This topic is sure to receive a great deal of attention in the years to come.

If the patient exhibits dysmorphic features along with hearing loss, testing may begin with array CGH followed by exome sequencing if the array CGH test is negative. If the geneticist suspects a specific syndrome, a molecular test specific for that syndrome may be ordered. This may involve a panel if it is a syndrome with multiple causative genes. Molecular tests for a specific syndrome are generally more cost-effective than sequencing techniques, but if results continue to be negative, exome sequencing may be warranted. A diagnosis is invaluable for patients who have significant health problems.

Once all tests have been exhausted, a negative result can be discouraging for a patient who stands to benefit from a genetic diagnosis. For these patients, audiologists may revisit the topic every 3 to 5 years and suggest a new genetics evaluation. Testing methods evolve quickly. A patient who received a negative result a few years ago may now be eligible for a test that either was not available previously or was too expensive. If the patient or the family still desires and could benefit from a genetic diagnosis this may be welcomed.

CONCLUSION

Audiologists are central figures in the health care teams treating patients with hearing loss. Since as many as 75-80% of early-onset permanent hearing losses are genetic and most adult-onset permanent hearing losses probably have a genetic component, it is imperative audiologists have a basic understanding of genetics if we are to fully serve our patients. Audiologists need not be genetics experts, but should understand when a genetics referral should be proposed and should be comfortable discussing this topic with their patients. Genetic testing has limitations and potential negative consequences which must be considered. The benefits of testing should outweigh the risks. If a patient is willing to complete a genetics evaluation, the geneticist and/or genetic counselor will determine if genetic testing is appropriate. To locate a genetic counselor, visit the National Society of Genetic Counselors at <https://www.nsgc.org> [118].

Completion of the Human Genome Project has allowed for the identification of thousands of genes, including many new genes found to be associated with deafness/hearing loss. As technology advances, more patients are able to receive a genetic diagnosis, and the tests continue to become faster, cheaper, and more sensitive. While new genes are sure to be linked to hearing loss in the future, genetic research is beginning to shift toward bioinformatics. Bioinformatics marries biology with computer science. Sophisticated software is used to analyze biological data and make predictions about their functions. This means that many research studies are moving out of the laboratory and onto the computer. Bioinformatics analyses may include predicting whether a gene mutation will cause deleterious protein function, predicting how a protein will fold, or examining how two different genes interact with one another. These studies will add new layers of complexity to our understanding of genes and how they function. In addition, our understanding of adult-onset hearing loss, to include presbycusis and noise-induced hearing loss, is bound to expand. Limited studies have

suggested genetic determinants may influence our susceptibility to noise-induced hearing loss. It has been recognized for decades that individuals respond differently to noise exposure. Genetic polymorphisms or gene-environment interactions may help explain this phenomenon and could lead to noise protection recommendations customized for each individual. Likewise, presbycusis (age-related hearing loss), known to vary widely across the population, may have more to do with genetic differences than the aging process itself. The decades to come are sure to deliver exciting new discoveries in the world of genetic hearing loss.

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Chapter 32

AUDIOLOGICAL AND SURGICAL OUTCOME AFTER COCHLEAR IMPLANT REVISION SURGERY

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ABSTRACT

Cochlear implantation is now widely accepted as a safe and effective treatment for children and adults with profound deafness. As with all electronic devices, a cochlear implant (CI) is susceptible to breakdown or failure. Although the CI reliability rate is now very high, the continually increasing population of implant recipients will result in the continued need for revision surgeries. The first report of a CI revision surgery occurred in 1985, by Hochmair-Desoyer and Burian. Since then, several reports have addressed the safety of this procedure, including the preservation or increase of speech perception performance, although there have also been reports of decreases in electrode activation, decreased speech perception and intra cochlear trauma, suggesting that cochlear reimplantation may have negative functional consequences in some patients, requiring careful consideration of the expected indications and benefits. This paper will review causes of revision surgery, how to diagnose cases of failed CI and will discuss surgical and audiological outcome of revision CI surgeries. Speech recognition ability with a replacement CI may significantly increase or decrease from that with the original implant. Experienced CI patients facing reimplantation must be counseled regarding the possibility of differences in sound quality and speech recognition performance with their replacement device.

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Keywords: cochlear implant failure, revision surgery, surgical outcome, auditory performance

INTRODUCTION

Cochlear implant (CI) surgery began over 30 years ago. During the subsequent decades, auditory performance has improved, resulting in broader implantation criteria. As the number of implanted patients grows and the lifespan of devices is outlived, an increasing number of device failures are expected. In consequence, the odds of ensuing complications are higher. Therefore, analyzing performance and complications after revision cochlear implantation is of the utmost importance [1].

Revision surgery has always been cause for concern because of the potential risk of creating greater damage to delicate inner ear structures when removing the original device and replacing it with a new one. Moreover, there is the fear of not being able to follow the path of the original electrode and achieve the same depth of insertion. Lastly, there is the possibility that functional performance will not be restored to levels achieved prior to device failure. This is of particular concern for the pediatric population in view of the fact that most children with CIs are pre linguistically deafened and are in the process of developing spoken communication skills. Disruption of sound input in the short term coupled with potential decrements in performance are serious consequences for the child requiring revision implant surgery. Owing to these potential adverse effects, investigating the prevalence of revision surgery and performance outcomes remains essential to clinical practice [2].

CAUSES OF REIMPLANTATION

Causes for reimplantation follow the classification proposed by Zeitler [3]. They include hard failure, soft failure, device infection or extrusion, improper initial placement, wound or flap complications, and upgrade of cochlear implant technology.

Device Failure

Hard failure occurs when there no auditory stimulation resulting from a confirmed malfunction of a component of the cochlear implant device; this might result from head trauma especially in children preventing communication between the internal and external components. Hard failures may be heralded by a sudden failure or an abnormal sound and no link to the processor. It is diagnosed by failed integrity test [3].

Soft failures are typically more challenging to recognize because the recipient has improved hearing compared to preimplantation and many factors are known to affect growth of auditory skills. Among all CI recipients, improvements in speech perception and localization varies widely across individuals Tyler et al. [4].

Table 1. shows check list symptoms for soft failure in both young children and adults

Young children	
A- behavioral	• Increase in bad behavior • Aggressiveness • Un willing to wear device • Inattentiveness • Regression in speech/language
B-teacher\therapist concern	• Intermittent responsiveness • Frequent appearance of being off task • Deterioration of school performance • Plateau in performance • Failure to meet appropriate expectations
C- other factors	• Educational placement • Type and amount of therapy • Familial involvement • Puberty
Older children/adults	
A-auditory	• atypical tinnitus • buzzing • roaring • engine like noise • static • popping
B-non auditory	• pain over implant site • pain down neck • shocking • itching • fascial stimulations
C-performance	• sudden drop in performance • decrement in performance over time • failure to meet expected performance • intermittent performance
D- mapping	• change in levels over time • changes in pulse width\duration • loss of channels • type and amount of therapy • change in impedance • shorts/open circuits
E-hardware	• replacements of all externals
F-objective assessment	• surface potential testing • neural response measures • evoked potentials • stimulus artifact

Symptoms of soft failure can be subtle and include decreased performance and speech perception, poor performance relative to expectations based on preimplantation characteristics, aversive stimuli causing subjective discomfort or pain especially at low stimulation levels, and hearing static while the device is off. A frequent need for reprogramming or difficulty programming often mis-attributed to complicated patients may

be related to the device. A strong index of suspicion may be needed to detect accompanying signs [5].

Balkany TJ et al. [6] suggested a checklist to evaluate soft failure in both children and adults.

Scalp Infection

Device infection may appear in the form of redness and fluctuation of the skin located over the receiver stimulator or an ulcerated wound. Once an infection or exposure of the device is suspected, antibiotics should be initiated immediately. If the infection persists, the explantation of the device is recommended.

According to Cohen [7], minor scalp flap complications are those that require minimal treatment or no treatment. They are less frequently reported than major complications. Signs of flap infection should be immediately recognized and treated. Local symptoms and signs include erythema, warmth, and drainage and crusting at the incision site.

Major scalp complications, include flap necrosis is often the result of poorly planned/executed incisions or flap designs. In patients with previous post auricular or face-lift incisions consideration should be given to modifications of the standard anteriorly based, C-shaped flap, as the blood supply to the flap may be inadequate. A “lazy S,” straight, or inverted U- or J-flap have been proposed to improve survival of the flap. Infection and/or underlying inflammatory conditions (e.g., vasculitis) may also predispose to flap necrosis and problems with wound healing. There have been case reports acclaiming the use of hyperbaric oxygen to speed recovery/healing and even to “prepare” the bed for rotational flap.

Electrode Extrusion

Extra cochlear electrode extrusion is also an indication for revision surgery and may be suggested by a decline in speech perception for which there is no alternative explanation. After device-related indications, it is the most common cause of need for re implantation in children [8].

The exact etiology is unknown, but it may be related to initial misplacement, cochlear ossification, aggressive host inflammatory responses to the implanted biomaterials, or physical forces placed on the cochlea that pull the electrode out of position. This latter circumstance might manifest with a progressive decline in performance over time. Despite the intuitiveness of this theory as it relates to skull growth in patients implanted when they were young children, studies have not documented electrode migration in the developing pediatric population. The slow decline in speech perception found in these patients before revision CI suggests that extrusion may be a dynamic process that can progress.

Some theorize that the use of perimodiolar electrodes which are stable by hugging the modiolus may decrease the likelihood of electrode extrusion. Additionally, tightly packing the cochleostomy site may aid in keeping the electrode in place [9].

Cochlear Implant Electrode Misplacement

The standard location for insertion of the CI electrode array is into the scala tympani of the cochlea. Failure to insert the electrode array into the scala tympani has been documented in the literature [10]. This can range from misplacement of the electrode array into the vestibule or internal auditory canal, placement into scala vestibuli or scala media or, more commonly, translocation of an array that is initially placed in scala tympani into the scala media or vestibuli as the electrode array advances apically. Fortunately, misplacement of the electrode array into extra cochlear locations (e.g., vestibule) considered to be a major complication is rare.

Inner ear malformations increase the likelihood of electrode array misplacement. Preoperative radiographic examination should help to avoid such complications. Yet, a normal preoperative CT scan does not exclude inner ear malformation that could lead to misplacement of the electrode array, such as malformation of the osseous spiral lamina. In addition, incomplete ossification of the tympano meningeal fissure (Hyrtl's fissure) that usually occurs by the 24th week in utero can result in permanent patency and provide another potential route for extra cochlear misplacement of the electrode array.

Jain and Mukherji [11] reported that the electrode array may be misplaced into the middle ear cavity, mastoid bowl, cochlear aqueduct, petrous carotid canal, Eustachian tube, or may be only partially inserted into the cochlea. The electrode may also be inserted into the vestibular system, most commonly the superior or lateral semicircular canal. Therefore, vestibular symptoms that are associated with cochlear implantation should arouse suspicion of electrode array misplacement. In addition, electrode array malposition should be considered in all cases when no benefit is achieved, and should be evaluated both by device-integrity testing and CT imaging, even in the setting of late presentation weeks after implant surgery.

Beyond extra cochlear misplacement; electrode array misplacement within the cochlea can also reduce overall performance. since clinical functional outcome would be expected to be quite different. Regarding mal insertion of cochlear electrode within the cochlea, various patterns have been recognized [12].

1. Tip Rollover. Some newer, peri modular electrode arrays are particularly prone to a tip roll-over and in these cases intraoperative imaging is helpful to confirm appropriate placement [13].
2. Over insertion of array: placing it deeper into the cochlea than desired, resulting in absence of electrodes in the proximal basal turn of the cochlea where high-frequency information is typically delivered.
3. Atwist in the electrode, the electrode bends or twists over on itself.
4. partial electrode insertion, electrode not inserted completely.
5. Translocation of the electrode array into scala media or vestibuli: This complication is relatively common, especially for electrode arrays placed deep in the cochlear apex. It is associated with increased scarring/fibrosis, neural degeneration, and diminished performance [14].

Magnet Displacement

A potentially problematic complication after cochlear implantation is the migration or displacement of the internal magnet. For older implant models in which there was a ceramic case that houses the internal receiver, this is not an issue. The advantage of having a removable magnet stems largely from the possibility of obtaining postoperative magnetic resonance imaging (MRI) scans. In a simple outpatient procedure, the internal magnet can be removed, scan obtained, and the magnet replaced. As compared with MRI-compatible implants without a removable magnet, the quality of an MRI of the head in a patient with an implant with the magnet removed is far superior [15]. To facilitate MRIs, most newer model implants contain removable magnets; however, it is possible that these removable magnets are more prone to dislodgement.

In the most common scenario, a child sustains some trauma to the skull overlying the receiver, thereby causing the magnet to literally pop out of its bed within the housing. Children are likely at greater risk for this than adults as a result of their developing motor skills and associated play activities and thinner scalps. In such a scenario, the patient may notice a lack of function of the implant or a hard lump just underneath the skin adjacent to the scalp.

When a displaced magnet is encountered, the patient or family should be counseled to not wear the device until the magnet can be replaced as a result of the risk for injuring the skin flap. Fortunately the repair of the problem is relatively straightforward. In rare cases, if the magnet becomes dislodged on multiple occasions and there is a tear in the Silastic ring holding the magnet in place, the entire implant may have to be replaced [16].

SURGICAL STEPS

After detection of a problem with the CI device, all efforts will be made to reimplant within the shortest time feasible. The surgery should ideally be performed by an experienced CI team.

In cases in which anatomy is preserved, re implantation is typically surgery performed following the same surgical steps. After skin incision and elevation of the skin flap, dissection should be done meticulous to try and preserve the physical integrity of the electrode array, which is encapsulated in a fibrous sheath. The lead is followed to the facial recess, round window and cochleostomy site; if present, are identified. If the implant is being removed and the reimplantation is being staged for a later date (e.g., in cases of infection), the array lead is cut as close as possible near to the posterior tympanotomy. This enables removal of the implant body and proximal electrode lead, without tension on the intra cochlear array and the risk of either inadvertent electrode removal or trauma to the cochlea. In such staged cases, the intra cochlear electrode lead is left in situ as a stent to preserve a tract for subsequent implantation.

If the cochlea is to be reimplanted with a new device at the same time (e.g., a device failure), the area around the cochleostomy is prepared in advance of the array change. Generally the implanted array can gently be withdrawn from the cochlea under microscopic visualization. If necessary, an incision can be made into the fibrous sheath that had formed

around the old electrode array. The new device is positioned the pocket under the scalp [17] and the new array is inserted carefully without disruption of the fibrous sheath. It is important to note that ideally the diameter of the new electrode array should be the same diameter or smaller than the original one. Rarely, there may be intra cochlear ossification or fibrosis that obscures the electrode tract. If so, this is often encountered around the cochleostomy and can be removed with micro rasps, picks or even a small diamond burr.

After the old array was removed, it was used for biofilm research [18], while the body and the attached lead were sent back to the manufacturer for cause-of-failure testing. If reimplantation is not planned at the same procedure, we left the electrode in the cochlea as a stent to prevent cochlear ossification and to facilitate reimplantation in the future.

Regarding insertion depth, reinsertion is usually a smooth step and results in a full insertion of the electrode array, but partial reinsertion may occur [19, 20]. Use an electrode array that is smaller or equal diameter of original one may help mitigate the risk of partial insertion.

If resistance to insertion is high, it would be wise to use straight electrode or styleted array because these are stiffer and may overcome resistance when it is encountered.

The implant team should develop a surgical contingency plan if reinsertion is not possible. For example, intervening ossification and/or intra cochlear granulation tissue may prohibit reinsertion of the new electrode. The surgeon should not first propose the question, "Can we implant the other ear?" in the operating room. Rather, the implant team should evaluate the suitability of the contralateral ear before revision surgery and counsel the patient accordingly. In cases of soft failure not associated with adverse stimuli, implantation of the contralateral ear may obviate removal of a functional device.

SURGICAL OUTCOME

Insertion of an electrode into the scala tympani often causes trauma to the spiral ligament and basilar membrane in the area of the basal turn [21]. Many histologic studies have indicated that while cochlear explantation followed by reimplantation can result in additional cochlear trauma in some cases, the trauma does not preclude successful use of the device [22].

Insertion of an electrode into the scala tympani often causes trauma to the spiral ligament and basilar membrane in the area of the basal turn [23]. However, surgical trauma to an already damaged cochlea does not appear to affect neural stimulation or auditory performance with an implant [24, 25]. Mounting evidence suggests that stimulation of remaining neural elements occurs at the level of the spiral ganglion cells or higher up the auditory pathway, because some patients with no hair cells or dendrites and markedly reduced spiral ganglion cell counts have received substantial benefit from their cochlear implants.

Greenberg et al. [26] reported in guinea pig that there was no significant difference in pathology of single implanted or reimplanted cochleae.

Jackler et al. [27] reported that cochlear explantation followed by immediate reimplantation may be not accompanied by damage to cochlea or its neural population. However, in cases with marked granulation tissue proliferation at round window and scala tympani, incidence of trauma is high.

Shepherd et al. [28] reported the histopathologic change after cochlear reimplantation using long multichannel intra cochlear electrodes in the macaque, where electrode insertion trauma involving the osseous spiral lamina or basilar membrane was greater in the reimplanted cochleae and also resulted in more extensive loss of basal ganglion cells, particularly when proliferation of granulation tissue at the cochleostomy was identified.

Linthicum et al. [29] reported that reimplantation histopathology showed marked new bone formation fibrous tissue and low count of spiral ganglion cells compared to single implanted cochlea.

Fayad et al. [30] reported that new bone formation around electrode especially greatest in scala tympani of basal turn and spiral ganglion cell count was marked reduced representing less than 10% of normal spiral ganglion cells.

Li et al. [31] by using a scoring system for damage to the lateral cochlear wall and a three-dimensional reconstruction method reported that marked level of new bone and fibrous tissue formation with cochlear re implantation. In addition they reported that insertional trauma to lateral cochlear wall play an important role in subsequent fibrosis and neo ossification following implantation and reimplantation. They also reported high levels of osteoprotegerin within the spiral ligament which may serve to inhibit bone remodeling and exposure of the underlying endosteum which may provide a nidus for inflammatory process to enhance ossification and inflammatory mediators may contribute to general increase in new bone formation.

The complications of cochlear reimplantation surgery can be summarized as follows:

1. Incomplete Electrode Extraction During Cochlear Implant Revision; Although the majority of revision operations are completed without complication, the current report demonstrates that one cannot universally assume that complete extraction of an indwelling cochlear implant electrode array will be straightforward. Kang et al. [32] reported 3 cases in which incomplete electrode removal with fracture of distal part of it inside cochlea and authors attributed that due to dense fibrous and bony tissue response at the cochleostomy site that extended into the cochlea. It is possible that, in some pediatric patients, a robust inflammatory response results in a fibrous and/or bony sheath that completely encases the array and fixes it within the cochlea, additionally, some patients had cochlear implants with intra cochlear positioners, which are designed to achieve juxtamodiolar positioning by displacing the array against the medial wall of the cochlea. It is possible that the shim like effect of the positioners contributed to the difficulties encountered during extraction of the electrode.
2. C.S.F leakage; was considered the the sole complication encountered during revision surgery in the past as reviewed by Lassig et al. [33] who reported 1 intraoperative outflow of CSF as the only surgical complication in 61 revision operations. Similarly, Buchman et al. [34] reported 1 instance of CSF leakage in 33 revision operations. Fayad et al. [35] also reported 2 occurrences of CSF leakage in 43 revision operations. Excessive cerebrospinal fluid (CSF) can access the cochlea through patent developmental pathways of the otic capsule or after traumatic disruption of the temporal bone.
3. facial nerve injury; Facial nerve injury risk is also high in revision and re-implantation surgery. Presence of fibrosis in the mastoid bowl, which requires

meticulous dissection with careful avoidance of the facial nerve to free the original electrode array. Adequate irrigation in order to prevent thermal injury is also important. The surgeon should be cautious about atypical positioning of the facial nerve in labyrinth abnormality cases [36].

4. Injury of the annulus or bony external auditory canal skin; due to marked thinning of canal in revision cases to identify anatomical landmarks will lead to cholesteatoma if it is not adequately repaired, retraction pockets and lastly protrusion of electrode through external auditory canal [37].
5. Perilymphatic fistula; through a cochleostomy and insertion trauma to the labyrinth may lead to postoperative vestibular problems. In addition, a serous labyrinthitis caused by electrode placement in the cochlea was suspected as being the possible etiology for vertigo in CI patients [38].
6. Acute mastoiditis, post traumatic wound breakdown and receiver-stimulator/magnet displacement occurred also as complications of revision surgery which are similar to primary surgery [39].

AUDIOLOGICAL OUTCOME

Cochlear implantation has been proven to be very effective surgery in rehabilitation of prelingual deaf children and post lingual deaf adult, but for some reasons, removal of cochlear implant may be required. For both child and family, it is a stressful condition as patient will undergo repeated surgery, a period of nonuse, and a period of rehabilitation again. There is also a greater concern about complications such as reduced performance following repeated surgery.

Here we will discuss audiological performance following revision cochlear implant surgery starting by impedance.

Although reimplantation is an undesirable consequence of cochlear implantation, many studies have shown good post-reimplantation results in terms of speech-perception scores [40, 41]. Only a few studies have reported patients who did not achieve the same perception scores after reimplantation [42].

In most, if not all, published studies, the period between first implantation, occurrence of the defect, and subsequent reimplantation was fairly long. For that reason, in most cases, a newer type of implant or another brand had become available and was implanted instead of the device that was initially used [43]. As a result, the newer device was an upgraded version of the former device and was coupled with improved software to drive the new implant. Hence, those changes in design, brand, or software could be the explanation of the same, or even better, speech-perception scores. Consequently, the confounding variable of a different type of implant weakens the comparison between speech-perception outcomes from the first implantation and the reimplantation.

Impedance

Impedance is a measure of electrical resistance at the electrode. it depends upon design of electrode, including materials used, surrounding tissues, fluid through which current exist and the electrode location into cochlea [44].

It can be increased by amount of cell cover and fibrous tissue growth around electrode array. As a result of repeated surgery there is increase in scar tissue formation and new bone and ossification. Thus increased impedance can be used post-operative as marker or proxy for increased inflammation [45]. High impedance is of clinical concern because it can cause saturation (compliance) of electrodes and reduce the dynamic range of stimulation.

Reduction in electrical impedance of cochlear implant electrodes is important as less energy is used, and this prolongs the cochlear battery life. Lower impedance with lower current allows for more focused stimulation of the neural elements in the cochlea, giving greater differentiation of sounds [46].

Neuburger et al. [47] found that increases in impedance are often accompanied by clinical inflammatory precipitation, with exudate and labyrinthitis and this can be in some cases of revision not all cases due to new bone formation with accompanying fibrosis.

Measurement of impedance will be conducted at time of surgery to identify very high impedance(open circuit) which is indicative of break in the wire lead, damage of electrode contact point, air bubbles around electrode contact, electrode malposition either (incomplete insertion or delayed extrusion) and ossification of cochlea fibrosis and inflammation, or low impedance (short circuit) which is indicator of one or two electrodes share a common electrical course, or partial short circuit which means that impedance decreased over time but failed to reach a value that will be flagged by software as a short circuit [48].

Steroids can decrease impedance levels and are used in hearing preservation techniques and cases with cochlear explant and reimplant which result in impedance elevation, although the duration of protection, areas of cochlea protected, and the best mode of delivery is still under investigation [49].

Speech Recognition

Does cochlear reimplantation affect speech recognition?

As electronic devices, cochlear implants are occasionally subject to damage or breakdowns. Obviously, in the event that a cochlear implant becomes unusable, reimplantation becomes necessary. Doubts may arise in the patient about his subsequent speech recognition performance with a new implant.

Hamzavi et al. [50] recently demonstrated substantial benefits in patients in whom an analogue single-channel implant was upgraded to a digital multichannel device. In that study, he observed that, 3 months following reimplantation, five of seven patients achieved speech recognition performance at about the same level experienced with the original implant. A decrease in speech recognition was noted in one subject only, and was related to her central auditory system.

Henson et al. [51] evaluated a group of 28 patients (Nucleus 22 cochlear implant) who were reimplanted. 37% of patients achieved significantly higher sentence or word scores with their replacement cochlear implants than with their original implants, while 26% showed no

significant change. The reason for the decline in speech recognition in that group was unclear, and parameters such as insertion depth or surgical complications did not seem to be relevant.

Parisier et al. [52] analyzed the outcomes of cochlear reimplantation in 25 children provided with Nucleus 22 cochlear implants. They found that open-set speech recognition scores and speech perception abilities remained stable or improved compared with results before reimplantation.

Balkany et al. [53] also found the speech recognition scores following reimplantation to be at least as good as with their initial implant. To achieve further beneficial audiological performance upon reimplantation, it appears that the same conditions which were applied to the initial implantation, such as insertion depth, implant type, and number of active channels, might be important indicators, as described by Miyamoto et al. [54].

Manrique et al. [55] reported a study on 38 patients requiring reimplantation and found that aided pure-tone hearing thresholds improved in 44% of the reimplanted patients, with 11% showing no change in their threshold. 64% percent of the patients showed an improvement between 20% and 35% points in their disyllabic word recognition score after reimplantation, with a further 9% showing no change in their speech recognition scores (SRS) from before to after reimplantation.

Rivas et al. [56] reviewed 34 patients who underwent cochlear reimplant, scores after reimplantation were better in 65% of cases, the same in 32%, and worse in 3%, when compared with the score obtained just prior to reimplantation.

Mahtani et al. [57] reported 32 reimplantation surgeries for 30 patients and reported that For the 25 adults with available scores in the quiet condition, 56% had no change in scores after reimplantation, 36% had improved scores, and 8% had poorer scores. For the 16 recipients tested in noise, 50% demonstrated no significant difference after reimplantation, 25% obtained significantly better scores, and the 25% obtained significantly worse scores.

CONCLUSION

Although cochlear implant surgery has been proven as a safe and effective method in rehabilitation of postlingual deaf adult and prelingual deaf children, these devices are subjected to damage, breakdown, need to upgrade and failure. in such cases, reimplantation is necessary. Although surgical problems leading to revision surgery and reimplantation are expected to diminish by experience, every center has to deal with device failures. Both revision surgery and reimplantation require extra care and it should be better carried out by experienced surgeons. Implant performances are expected to be comparable with primary implantations and a lot of studies showed improve audiological outcome after reimplantation.

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Chapter 33

POSTUROLOGY: THE SCIENTIFIC INVESTIGATION OF POSTURAL DISORDERS

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ABSTRACT

The human posture, regulated by the tonic postural system in response to the phenomenon of the force of gravity, is organized by feedback and feedforward processes according to a non-linear cybernetic system in which the central nervous system integrates sensory inputs from interoceptive, proprioceptive and exteroceptive organs modulating the muscular tone. According to this scheme, afferences from sensory organs such as the muscular proprioceptors organs, the stomatognathic apparatus, the visual system as well as the auditory and the vestibular system are responsible for controlling balance and postural control. If one of these postural receptors is dysfunctional (i.e., it

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does not function physiologically), it sends aberrant informations to the central nervous system, which modulates a response that generates an adaptation of the muscular tone through muscle chains according to a non-linear dynamic relationship. The posturography, comprising the baropodometric evaluation and the stabilometric assessment, is an instrumental evaluation that allows, through a platform, to measure body posture. In particular, pressure and plantar surface contribute to provide fundamental postural characteristics, whereas, the study of the centre of pressure (i.e., the point of the load pressure sum of the ground reaction force vector) is used to evaluate body balance and postural control.

The purpose of this chapter is to understand the main features of human posture and how it is possible to analyze it.

Keywords: posture, stability, body balance

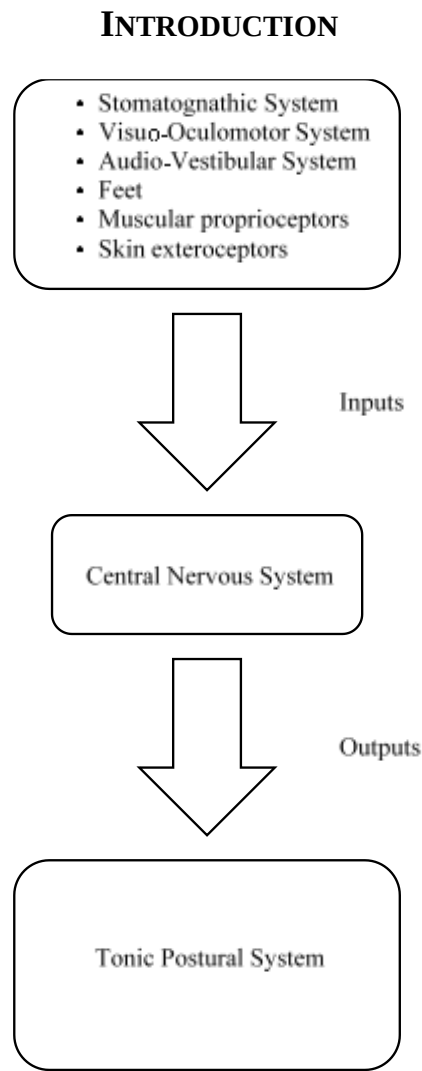


Figure 1. The non-linear cybernetic system of the human posture.

The Posturology is the science that studies human posture in static and dynamic and the relationship existing between body segments. The human posture can be represented as a non-linear cybernetic system that is regulated by the tonic postural system, antigravity musculature which allows to control body stability subject to the force of gravity. Indeed, the muscle apparatus maintains a basal activity, called tone, in order to react to the force of gravity without performing changing on physical location or movements of skeletal parts of human body [1].

Body posture is influenced by afferents from sensory receptors as the stomatognathic system, the visual apparatus, the audio-vestibular system, the feet, the muscular proprioceptors organs, the skin [2-8]. As represented in the Figure 1, these organs project sensory information into the central nervous system that integrates the afferents and processes a response to the tonic postural system [1]. A change in the inputs from these systems due to a physiological decline or a pathological condition causes adaptation mechanism through the muscle chains causing altered effects on body balance [9-14]. Moreover, it is important to note that, according to the non-linear dynamic relationship, cause and effect could not correspond in terms of proportion and for a small phenomenon could be present a major consequence.

In case of altered sensory information from a postural receptor the tonic postural system responds changing muscular activity modulating the tone leading adaptation mechanisms as long as it is possible until the postural disorder.

The role of the posturologist is to evaluate body balance and posture features, in qualitative and quantitative manner, in order to understand the cause of a possible postural disorder.

HUMAN POSTURE EVALUATION

Body posture assessment comprehends: patient history acquisition, visual postural analysis, postural clinical tests and the posturography (including baropodometric assessment and the stabilometric assessment).

PATIENT HISTORY

An accurate patient history obtainment facilitates the identification of the cause of the postural disorder. Accordingly, the inquiry should provide elements of knowledge about: trauma, accidents, injuries as well as previous surgical operations, allergies/intolerances, pains but also diseases/impairments and/or taking drugs, treatments in progress, sight or hearing loss, audiovestibular characteristics as the presence of tinnitus, vertigo/dizziness, aural fullness [15-22]. Furthermore, the posturologist should collect data regarding lifestyle features as sleep quality, stress or anxiety state, physical activity level and type of job, important contributors that determine human posture [23-29]. Moreover, it was widely investigated in the literature the role of occlusal or orthopedic devices on human posture, for this reason for the expert in posturology it is important to annotate also these informations [30-32].

VISUAL POSTURAL ANALYSIS

The observation of the posture is an essential part of the body posture evaluation. This qualitative assessment takes into consideration the spatial location of peculiar points of the body in order to analyze any deviations respect to the vertical line for the sagittal and the frontal plane and possible rotations in the horizontal plane [33]. Moreover, it is possible to examine the alignment of body segments and the differences between rightward and leftward hemibody [33].

For the visual postural analysis the subject is asked to maintain the orthostatic stance as comfortably as possible wearing only underwear, barefoot and looking forward while the posturologist records the location of the landmarks for all the anatomical planes as represented in the figures 2,3,4. In particular, in the frontal plane the following lines are considered: the bipupillary line, the connection line of acoustic meatus, the line connecting left and right labial commissures, the bi-acromial line, the bi-styloid line and the bi-ischial line (Figure 1). In absence of any postural disorder, all these reference lines should be parallel to each other. To assess postural features in the sagittal plane, the alignment of peculiar points passing through the vertical axis, i.e., the acoustic meatus, the odontoid process of the second cervical vertebra, the body of the third lumbar vertebra and the lateral malleolus, is taken into consideration (Figure 2). Moreover, the cervical curve of the spine should measure 6 - 8 cm and the lumbar curve 4-6 cm. In the evaluation of the horizontal plane the main reference lines concern the parallelism between the shoulder girdle and the pelvic girdle (Figure 3).

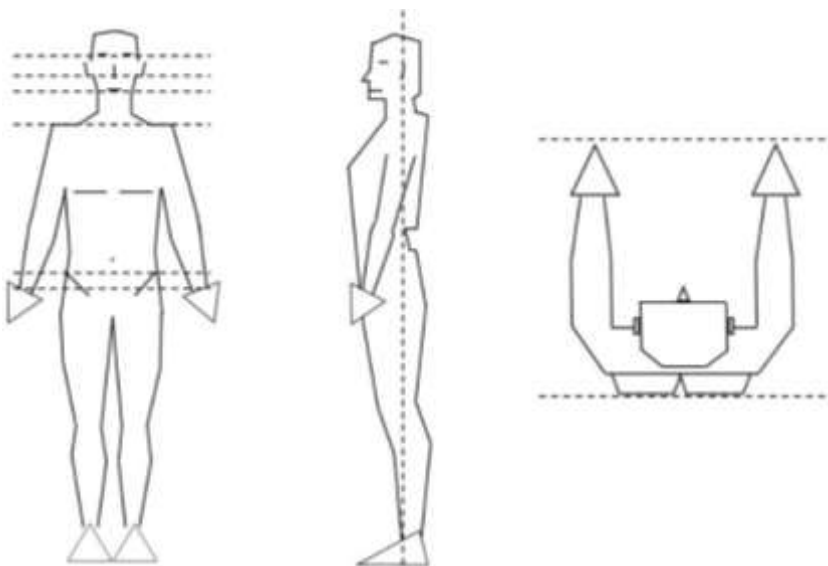


Figure 2,3,4. The visual postural analysis in the frontal, sagittal and horizontal plane respectively.

POSTURAL CLINICAL TESTS

Since, as mentioned above, all the postural receptors lead sensory information to the central nervous system influencing the tonic postural system, postural clinical tests are

performed to identify a dysfunctional postural receptor. Indeed, these tests allow the evaluation of the physiological function of the organs involved on postural regulation. Among these assessments, it is important to mention the ocular motility exam, the swallowing evaluation and the vestibular function tests.

POSTUROGRAPHY

Posturography, or instrumental postural assessment, includes a baropodometric test, an examination that allows the measurement of the foot pressure and the plantar surface and a stabilometric test, for the measurement of the regulation of the activity of the postural tonic system. Posturography is measured using a platform that samples real time postural sway at different frequency based on the type of the platform.

The baropodometry is measured in 5 seconds during which the patient maintains the orthostatic position on the platform with the head in a neutral position facing forward, the arms along the trunk and the feet positioned next to each other. The main features measured through this test are the load distribution between feet, the rearfoot/forefoot ratio of the load pressure for each foot and the plantar surface characteristics.

The duration of the stabilometry is 51.2 seconds and provides that the subject maintains the feet positioned side-by-side and forming an angle of 30° and both heels at 4 cm apart [34]. Basic, participant repeats the stabilometric test in two different conditions: with eyes open and then with eyes closed to examine the impact of sight on posture. Moreover, complementary stabilometric tests are used to investigate the influence of all the others receptors on stability, such as the test with caloric vestibular stimulation for the vestibule or the stabilometric assessment with mouth open to evaluate the effect of the stomatognathic system on postural control [35,36]. In the Table 1 are illustrated some methods to analyze the influence of sensory information from postural organs on body balance. The parameters considered for the postural sway are the coordinates of the center of pressure (CoP) and in particular the Sway Path Length (SPL), i.e., the path length of the center of pressure, and the Ellipse Sway Area (ESA), i.e., the surface that contains the movement of the CoP.

INTERVENTION PROGRAMS

As mentioned previously, a postural disorder is caused by an altered postural receptor. For this reason, if the posturologist identifies a postural disorder by posture evaluation, the treatment to rebalance the system depends on which receptor is in dysfunction. Furthermore, intercepted the receptor, the intervention can provide a wide range of approaches.

The role of the posturologist, in presence of a postural disorder, is to advise and direct the patient to visit the specialist (such as the gnathologist in case of swallowing disorder or the otorhinolaryngologist in presence of vertigo).

Anyhow, it is widely known that, within the various treatments proposed, physical activity is always recommended in order to improve balance [37].

Table 1. Some stabilometric tests for postural receptors

Visuo-Oculomotor System	With eyes closed With eyes towards different directions With prisms
Audio-Vestibular System	Caloric vestibular stimulation Galvanic vestibular stimulation
Stomatognathic System	With mouth open With occlusal splint

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Chapter 34

THE INFLUENCE OF OTOVESTIBULAR SYSTEM ON BODY POSTURE

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ABSTRACT

It is well-known that body posture is controlled by an integration, at the level of the central nervous system, of afferences coming from various organs that influences the tonic postural system responsible for the alignment of the skeletal body segment of the human body, for balance and for postural control. Many studies have shown that the auditory and the vestibular systems contribute significantly to posture. The scientific literature reported that patients suffering from hearing impairment or vestibular disorders may be affected by loss of balance or inability to maintain postural control. Furthermore,

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many researchers have demonstrated a significant correlation between hearing loss and the risk of falling. Non-physiological sensory information from the otovestibular system negatively interferes on posture inducing asymmetrical muscular tensions that determines postural disorders. In these patients, a postural sway analysis, using a stabilometric platform, and a gait analysis, through a dynamic baropodometric test, can be considered in order to measure their ability to maintain static and dynamic balance and to examine their potential improvement after an otovestibular rehabilitation. The aim of this work is to investigate the influence of hearing loss and vestibular disorders on body posture.

Keywords: body balance, vestibular disorders, hearing loss

THE OTOVESTIBULAR SYSTEM

Among the sensory organs, the otovestibular apparatus represents a complex system able to project to the central nervous system the sensory information concerning auditory, sense of position, and perception of movement in the space of the head in order to regulate appropriately static and dynamic body balance [1].

The cochlea is an auditory organ responsible for the transduction of mechanical waves into electrical signals that reach the central nervous system (CNS) through the cochlear nerve. Regarding the vestibular component, the afferents from this apparatus are integrated at the level of the central nervous system (CNS) in addition to the visuo-oculomotor and proprioceptive information. Consequently, the CNS produces efferent responses to the ocular muscles and the spinal cord, generating the vestibulo-ocular reflex (VOR) and the vestibulospinal reflex (VSR). The latter generates compensatory movements in order to regulate and maintain body balance, the former movements of the oculomotor muscles in base of changing head positions [1]. Both reflexes are fundamental to adjust and control body balance.

The cochlea as well as the vestibule are located in the inner ear and both sensory information coming from these organs influences human posture [2-6].

OTOVESTIBULAR SENSORY INFORMATIONS

Although it is well-known that all the sensory systems contribute to the regulation of posture and to the maintenance of balance, a physiological prevalence of discernment of sensory informations in correlation with age exists [7]. In particular, at birth, body posture depends mainly on labyrinthic and sound stimuli, whereas when the human being adopts a bipedal stance, the static postural control is managed above all by proprioceptive inputs from the foot and the paravertebral muscles instead, and for the dynamic postural control, from visual afferences. However, the scientific literature has demonstrated the importance of audio-vestibular sensory information on body posture in children as well as in elderly [8-12].

OTOVESTIBULAR DISORDERS AND BODY BALANCE

As the regulation of the activity of the tonic postural system and the ability to maintain body balance depends on all the sensory postural receptors, a physiological decline of the audio-vestibular system, hearing impairment, or vestibular disorders affect body balance [13-17]. In particular, hearing loss, the most common sensorial deterioration, has disadvantageous effects on the life quality and, among the adverse consequences, causes a possible alteration on body balance increasing the risk of falling especially in the elderly [18-21]. Likewise, it is widely recognized that, vestibular disorders such as tinnitus, vertigo, or dizziness have a significant impact on physiological and vital functions, and moreover, negatively influence postural control [16, 22-25].

In patients with damaging/disease of a sensory organ, the use of assistive devices, such as hearing aids or cochlear implants for the audio-vestibular system, can improve daily activities and, in general, the quality of life [8, 26, 27].

POSTUROGRAPHY: A QUANTITATIVE ASSESSMENT OF BODY BALANCE

The posturography allows the measurement of muscular activity of the tonic postural system. In these patients, this instrumental postural assessment is fundamental in order to measure their ability to maintain static and dynamic balance, and moreover, to examine any change after an otovestibular rehabilitation or a cochlear implant surgery [27-30]. In particular, by means of a baropodometric platform, it is possible to evaluate postural sway analysis, through a stabilometric test, and a gait analysis, through a dynamic baropodometric test [31].

Through the stabilometry it is possible to analyze the statokinesigram graph, i.e., the path of the center of pressure (CoP) and the surface that contains the movement of the CoP (the Sway Path Length (SPL) and the Ellipse Sway Area (ESA) respectively), and the stabilogram graph that shows the CoP displacement during the time distinguished by direction (backwards/forwards and medial/lateral sway).

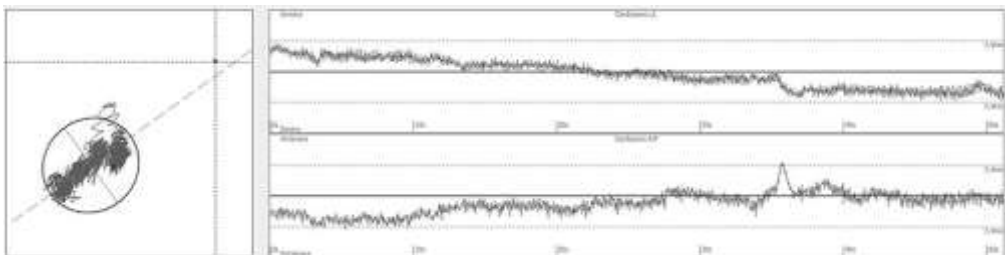


Figure 1. Statokinesigram (on the left) and stabilogram (on the right) of the stabilometric test.
http://posturografia.it/wp-content/uploads/2017/04/posturografia_11.jpg.



Figure 2. Stabilometric test.

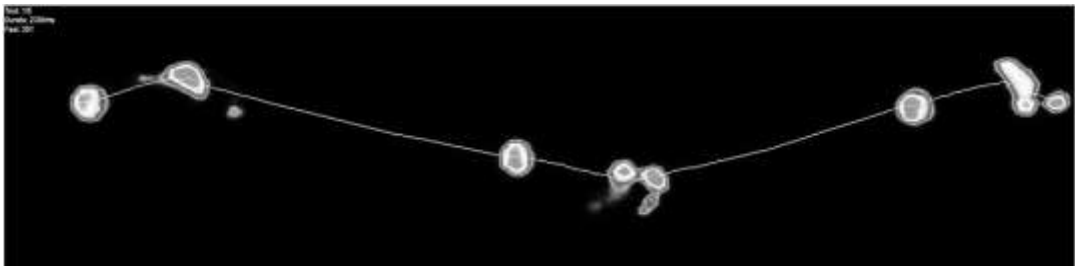


Figure 3. Study of the gait analysis through a dynamic baropodometric test
http://pedanabaropodometrica.it/wp-content/uploads/2017/05/pedanabaropodometrica_10.jpg.

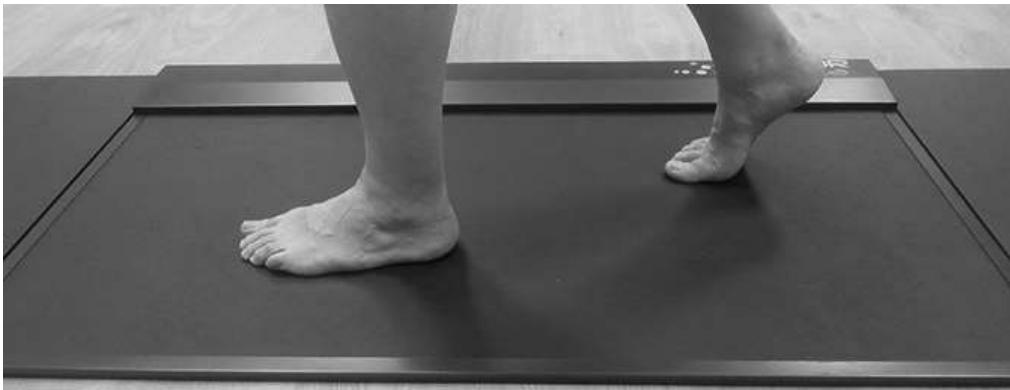


Figure 4. Baropodometric test https://www.sensormedica.com/site/images/pedana_120_50.jpg.

As sensitive and specific measures are a priority in order to detect vestibular disorders, Di Fabio has investigate the sensitivity and specificity of static and danicam posturography to identify these patients [32]. The author shows that the posturography, if applied in isolation,

turns out to be ineffective, in terms of sensitivity, to detect vestibular impairment. However, the association of posturography with the other vestibular function tests increased the sensitivity of identifying vestibular deficits from 61% to 89%.

INFLUENCE OF OTOVESTIBULAR SYSTEM ON BODY BALANCE

Many authors have investigated the impact of auditory stimuli, in terms of frequency, intensity, as well as sound duration, on body balance and the relationship between hearing loss and the risk of fall [7, 10, 14, 20, 21, 27, 29].

Although Mainenti et al. reported no significant differences on stabilometric parameters when subjects were submitted to different types of sound stimulation [33], contrarily, Raper and Soames [34] showed higher sway in sound conditions compared with no sound condition, with frequency stimulations at 250 Hz. In addition, a study by Park et al. reported that the Sway Path Length on the anterior-posterior axis increased with higher frequencies of sound [35]. Siedlecka et al. suggested that sound stimuli with frequencies from 1000 Hz to 4000 Hz influence body stability [3].

Many studies have examined the role of sound intensity on body posture and the results seems to indicate that sound intensity higher than 90 dB affects postural stability [3, 36].

As reported in the scientific literature, sound duration affects body sway [33, 37, 38]. In particular, Kapoula et al. performed a stabilometry for 51.2 seconds finding a significant affect of sound disturbances on postural sway in patients with highly modulated tinnitus [37]. Contrariwise, many researches reported no significant influence when the stabilometric tests were performed for 20 or 30 seconds [33, 38].

THE ROLE OF PHYSICAL ACTIVITY ON BODY BALANCE

The scientific literature reported that, among the intrinsic factors, falls are related to the physiological decline of hearing, hearing impairments and vestibular disorders [39]. It is well-known that, among the treatments, exercise improves balance ability that induces a consequent fall reduction, and proves to be an effective intervention of falls prevention, in particular for older people [40, 41, 42]. The literature seems to be in agreement that balance exercises appears to be the most efficacious type of physical activity in order to improve body stability [43].

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Chapter 35

AUDITORY BRAINSTEM RESPONSE AND FREQUENCY FOLLOWING RESPONSE IN PATIENTS WITH SICKLE CELL DISEASE

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ABSTRACT

The aim of this study was to analyze the auditory brainstem response (ABR) and frequency following response (FFR) in patients diagnosed with Sickle Cell Disease (SCD) who were referred to the outpatient hemoglobinopathy clinic at a public hospital in southern Brazil. Fifty-four individuals aged between 6 and 24 years [mean age $\pm$ SD (years), 14.1 ± 4.6] were evaluated. Pure tone audiometry, high frequency tonal audiometry, tympanometry, and transient evoked otoacoustic emission for determination of peripheral normality were performed; the overall results indicted normal auditory thresholds in all individuals. Subsequently, electrophysiological evaluations including ABR and FFR were performed; the analysis of the ABR responses revealed an alteration in 88.9% of the individuals and that of FFR in 98.1%. The achievement of auditory thresholds within the normal range and presence of otoacoustic emissions enabled but did not guarantee excellence in the auditory pathway of the evaluated individuals.

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Keywords: sickle cell disease, hearing, auditory evoked potentials, electrophysiology

INTRODUCTION

Sickle cell disease (SCD) is an inherited disease characterized by abnormality of the hemoglobin in the red blood cell. Hemoglobin is composed of proteins and iron which imparts a red color to the blood and allows the fixation of oxygen for transport to the cells of tissues and organs in the living organism. During periods of decreased oxygen tension in the red blood cell's environment, the abnormal hemoglobin content results in the transformation to a sickle cell pattern. The morphological and associated physiological changes drastically reduce the ability of the red blood cells to navigate and provide oxygen throughout the body [1].

The World Health Organization report indicates that SCD is a common disease, affecting approximately 5% of the world's population [2]. In Brazil, it is the most prevalent genetic disease, predominantly affecting individuals of Black/African ethnicity, with heterogeneous distribution among the regions. The diagnosis is made through the foot test on the 5th day of life [3]. The prevalence rate is approximately 6 to 10% in the north and northeast regions and at a lower rate of 2 and 3% in the south and southeast regions. The prevalence rate in Rio Grande do Sul is estimated at only 2% of the present population [4].

Due to the vaso-occlusive nature of SCD, there is potential for hearing damage. The relationship between SCD and peripheral hearing loss has been reported, but the studies reveal variable findings. Some reports have indicated that peripheral hearing loss is correlated with possible damage caused by low oxygenation of the cochlea in patients with vaso-occlusions through the disease [1, 5, 6]. Other reports have indicated that neurological symptoms could lead to central impairment [6, 7]. The discrepancies between studies could be due to the differences in audiological evaluation and incidence of hearing loss of 12 to 66% [6].

The auditory changes impact the individual's quality of life through the difficulty in analyzing sound information as well as overall communication impairment. There are no studies to investigate the speech-evoked ABR in this population; hence, research in this field is of interest.

This study aimed to analyze the ABR and FFR in patients diagnosed with SCD with normal peripheral auditory evaluation.

METHODS

This was an observational cross-sectional case series study of patients referred to the hemoglobinopathy outpatient clinic at a public hospital in Rio Grande do Sul, Brazil (southern region of the country). The study was approved by the Research Ethics Committee at the hospital where the study was developed (number 4448621500005327) and conducted under ethical principles that protect the rights, dignity, and well-being of the participants. Patients of the age group of 6 to 24 years were included. The exclusion criteria were the presence of clinically relevant comorbidities, quitting during the evaluation, and unilateral or bilateral peripheral hearing loss.

Table 1. Parameters and Range of Normality Considered for ABR and FFR

ABR		FFR		
Parameters Used				
Stimulus	click	Stimulus	syllable [da_40 ms]	
Number of sweeps	2 cycles 2048	Number of sweeps	3 cycles 1000	
Presentation	ipsilateral	Presentation	ipsilateral	
Rate	27.7/s	Rate	11.1/s	
Polarity	rarefied	Polarity	alternating	
Window	12 ms	Window	60 ms	
Intensity	80 dB	Intensity	80 dB	
Gain	100	Gain	150	
Low-pass filter	1.5 KHz	Low-pass filter	3.0 KHz	
High-pass filter	100 Hz	High-pass filter	100 Hz	
Rejection EEG	20%	Rejection EEG	30%	
Range of Normality Considered				
Measure	Latency (ms)	Measure	Latency (ms)	Amplitude (mV)
Wave I	1.11-2.07			
Wave III	3.30-3.98	Wave V	6.11-7.11	0.16-0.46
Wave V	5.25-5.89	Wave A	6.83-8.19	(-0.27)–(-1.03)
Interpeak I-III	1.91-2.19	VA Complex	0.51-1.27	0.41-1.53
Interpeak III-V	1.91-1.95	Peak C	16.73-18.65	(-0.18)–(-0.54)
Interpeak I-V	3.48-4.48	Peak F	38.51-40.95	(-0.24)–(-0.62)

ms, milisecond; dB, decibel; Hz, hertz; μ V, microvolt.

The sequence of evaluations was as follows: tonal threshold audiometry, high frequency tonal audiometry, tympanometry, transient evoked otoacoustic emission, ABR, and FFR (syllable /da/). Equipment used for the evaluations were: AC-40 (Interacoustics), AT235h (Interacoustics), Eclipse EP25 (Interacoustics), and SmpartEP (Intelligent Hearing Systems). The first four exams were used only to establish peripheral normality.

The parameters for obtaining recordings for both the uptake and range of normality for ABR and FFR are described in Table 1. The parameters were adapted from the equipment protocol [8] for ABR, and those of Russo et al. [9] and Gonçalves [10] for FFR. To determine the range of normality, two standard deviations of each measurement were considered, except for those for the amplitude of Wave V and Peak F that considered only one deviation due to asymmetry of the distribution under neural conduction. The tracings were analyzed and sent to two audiologists for judgment of the demarcation of the waves.

RESULTS

We evaluated 54 patients with a medical diagnosis of SCD, with mean age of 14.1 years. The sample was distributed in three age groups: twelve years-old (17 subjects, 31.5%); 12 to 18 years-old (24 subjects, 44.4%); 18 to 24 years-old (13 subjects, 24.1%). Twenty-four male individuals (44.4%) and 30 female individuals (55.6%) participated.

The ABR with click stimulus revealed a change in 88.9% of the sample, and the increase of absolute latency of waves III and V and interpeak I-III were predominant. There were no significant differences between the latencies obtained between the bilateral ears (Table 2);

however, there was greater impairment in the male individuals and age group of 12 to 18 years-old (Table 3).

Table 2. Comparison of ABR results between the bilateral ears

Variables	Right Ear	Left Ear	p
	Mean $\pm$ SD	Mean $\pm$ SD	
Wave I	1.78 $\pm$ 0.10	1.76 $\pm$ 0.14	0.167
Wave III	3.98 $\pm$ 0.16	3.98 $\pm$ 0.18	0.873
Wave V	5.90 $\pm$ 0.20	5.90 $\pm$ 0.17	0.844
I-III	2.20 $\pm$ 0.16	2.21 $\pm$ 0.17	0.303
III-V	1.92 $\pm$ 0.11	1.92 $\pm$ 0.09	0.931
I-V	4.12 $\pm$ 0.20	4.14 $\pm$ 0.19	0.365

SD, standard deviation.

Table 3. Comparison of changes in ABR results according to sex and age group

Variables	Ears	Total Sample	Female	Male	p
		n (%)	n (%)	n (%)	
click					
Wave I	Right	1 (1.9)	0 (0.0)	1 (4.2)	0.444
	Left	3 (5.6)	2 (6.7)	1 (4.2)	1.000
Wave III	Right	26 (48.1)	11 (36.7)	15 (62.5)	0.107
	Left	23 (42.6)	9 (30.0)	14 (58.3)	0.069
Wave V	Right	31 (57.4)	12 (40.0)	19 (79.2)	0.009
	Left	28 (51.9)	13 (43.3)	15 (62.5)	0.260
I-III	Right	30 (55.6)	11 (36.7)	19 (79.2)	0.004
	Left	35 (64.8)	15 (50.0)	20 (83.3)	0.024
III-V	Right	18 (33.3)	7 (23.3)	11 (45.8)	0.146
	Left	22 (40.7)	11 (36.7)	11 (45.8)	0.687
I-V	Right	3 (5.6)	1 (3.3)	2 (8.3)	0.579
	Left	3 (5.6)	0 (0.0)	3 (12.5)	0.082
WaveV interaural differencea	-	6 (11.1)	1 (3.3)	5 (20.8)	0.078
Global Modification	-	48 (88.9)	24 (80.0)	24 (100)	0.028
Variables	Ears	<12 years	12–18 years	>18 years	p
		n (%)	n (%)	n (%)	
Wave I	Right	0 (0.0)	1 (4.2)	0 (0.0)	0.529
	Left	2 (11.8)	1 (4.2)	0 (0.0)	0.350
Wave III	Right	8 (47.1)	14 (58.3)	4 (30.8)	0.276
	Left	8 (47.1)	13 (54.2)	2 (15.4)	0.068
Wave V	Right	10 (58.8)	17 (70.8)	4 (30.8)	0.062
	Left	8 (47.1)	14 (58.3)	6 (46.2)	0.694
I-III	Right	11 (64.7)	16 (66.7)	3 (23.1)	0.026
	Left	10 (58.8)	20 (83.3)	5 (38.5)	0.020
III-V	Right	3 (17.6)	11 (45.8)	4 (30.8)	0.165
	Left	6 (35.3)	11 (45.8)	5 (38.5)	0.781
I-V	Right	0 (0.0)	2 (8.3)	1 (7.7)	0.480
	Left	0 (0.0)	2 (8.3)	1 (7.7)	0.480
WaveV interaural differencea	-	1 (5.9)	4 (16.7)	1 (7.7)	0.503
Global Modification	-	15 (88.2)	24 (100)	9 (69.2)	0.017

n, number; aWave V interaural difference of latency of ≤ 0.2 ms is considered as normal.

The FFR showed a change in 98.1% of the sample, indicating worse Wave V latency for the left ear, and smaller amplitudes of Wave A and Peak F for the right ear (Table 4). There was no statistically significant difference between the sexes, but the latency of Wave A was later detected in the left ear in the age groups of ≤ 12 years old and 12 to 18 years old (Table 5).

Table 4. Comparison of FFR results between the bilateral ears

Variables	Right Ear	Left Ear	p
	Mean $\pm$ SD	Mean $\pm$ SD	
Latency V	7.10 $\pm$ 0.74	7.37 $\pm$ 1.04	0.018
Latency A	8.61 $\pm$ 0.95	8.89 $\pm$ 1.22	0.065
Latency VA	1.50 $\pm$ 0.56	1.52 $\pm$ 0.53	0.893
Latency C	18.6 $\pm$ 1.00	18.3 $\pm$ 1.25	0.269
Latency F	41.1 $\pm$ 1.34	41.5 $\pm$ 1.75	0.098
Amplitude Va	0.33 (0.25-0.44)	0.35 (0.27-0.46)	0.766
Amplitude Aa	0.19 (0.14-0.31)	0.29 (0.19-0.37)	0.004
Amplitude VAa	0.51 (0.41-0.74)	0.64 (0.48-0.80)	0.139
Amplitude Ca	0.26 (0.16-0.39)	0.29 (0.16-0.43)	0.287
Amplitude Fa	0.26 (0.20-0.40)	0.35 (0.25-0.50)	0.012

SD, standard deviation; a described by median (25-75 percentile).

Table 5. Comparison of the alterations of the FFR results according to sex and age group

Variables	Ears	Total Sample	Female	Male	p
		n (%)	n (%)	n (%)	
Speech-Evoked					
Latency V	Right	20 (37.0)	8 (26.7)	12 (50.0)	0.139
	Left	24 (44.4)	10 (33.3)	14 (58.3)	0.118
Latency A	Right	30 (55.6)	14 (46.7)	16 (66.7)	0.232
	Left	34 (63.0)	15 (50.0)	19 (79.2)	0.055
Latency VA	Right	29 (53.7)	15 (50.0)	14 (58.3)	0.737
	Left	33 (61.1)	18 (60.0)	15 (62.5)	1.000
Latency C	Right	22 (40.7)	10 (33.3)	12 (50.0)	0.337
	Left	17 (31.5)	8 (26.7)	9 (37.5)	0.578
Latency F	Right	26 (48.1)	11 (36.7)	15 (62.5)	0.107
	Left	29 (53.7)	15 (50.0)	14 (58.3)	0.737
Amplitude V	Right	4 (7.4)	2 (6.7)	2 (8.3)	1.000
	Left	3 (5.6)	2 (6.7)	1 (4.2)	1.000
Amplitude A	Right	34 (63.0)	19 (63.3)	15 (62.5)	1.000
	Left	25 (46.3)	16 (53.3)	9 (37.5)	0.376
Amplitude VA	Right	12 (22.2)	6 (20.0)	6 (25.0)	0.913
	Left	9 (16.7)	5 (16.7)	4 (16.7)	1.000
Amplitude C	Right	18 (33.3)	13 (43.3)	5 (20.8)	0.146
	Left	16 (29.6)	8 (26.7)	8 (33.3)	0.816
Amplitude F	Right	18 (33.3)	9 (30.0)	9 (37.5)	0.771
	Left	10 (18.5)	7 (23.3)	3 (12.5)	0.483
Alteration Conduction	-	53 (98.1)	29 (96.7)	24 (100)	1.000
Variables	Ears	<12 years	12 – 18 years	>18 years	p
Latency V	Right	7 (41.2)	11 (45.8)	2 (15.4)	0.171
	Left	9 (52.9)	13 (54.2)	2 (15.4)	0.053

Table 5. (Continued)

Variables	Ears	Total Sample	Female	Male	p
		n (%)	n (%)	n (%)	
Latency A	Right	12 (70.6)	12 (50.0)	6 (46.2)	0.313
	Left	13 (76.5)	17 (70.8)	4 (30.8)	0.021
Latency VA	Right	10 (58.8)	12 (50.0)	7 (53.8)	0.856
	Left	13 (76.5)	13 (54.2)	7 (53.8)	0.292
Latency C	Right	8 (47.1)	10 (41.7)	4 (30.8)	0.662
	Left	6 (37.5)	9 (37.5)	1 (7.7)	0.126
Latency F	Right	7 (41.2)	13 (54.2)	6 (46.2)	0.705
	Left	6 (35.3)	15 (62.5)	8 (61.5)	0.184
Amplitude V	Right	1 (5.9)	3 (12.5)	0 (0.0)	0.367
	Left	1 (5.9)	1 (4.2)	1 (7.7)	0.903
Amplitude A	Right	9 (52.9)	14 (58.3)	11 (84.6)	0.168
	Left	9 (52.9)	9 (37.5)	7 (53.8)	0.510
Amplitude VA	Right	4 (23.5)	5 (20.8)	3 (23.1)	0.976
	Left	2 (11.8)	4 (16.7)	3 (23.1)	0.712
Amplitude C	Right	3 (17.6)	9 (37.5)	6 (46.2)	0.220
	Left	7 (41.2)	5 (20.8)	4 (30.8)	0.371
Amplitude F	Right	4 (23.5)	9 (37.5)	5 (38.5)	0.584
	Left	5 (29.4)	4 (16.7)	1 (7.7)	0.301
Alteration Conduction	-	16 (94.1)	24 (100)	13 (100)	0.330

DISCUSSION

In the present study, the results of electrophysiological evaluation of hearing in patients with SCD were analyzed, and central alterations were revealed through both ABR and FFR.

Reports on the etiology and abnormal findings of ABR have indicated that several diseases may generate similar patterns of response, under condition of effects at the same level of the structure and function of the system [11, 12]. The increase in latencies to the click stimulus can therefore promote a brain stem lesion.¹³ In addition, reports have indicated that there is alteration of the central auditory processing associated with the increase of absolute and interpeak latency, and increased latency of the I-III interpeak of the sample indicative of the presence of a low brain stem lesion which is closely associated with auditory processing disorder [14, 15]. These findings may be due to the synaptic delay or delay in neural transmission through incomplete myelination and reduced synaptic efficiency [15].

The FFR is considered an excellent target method to detect central auditory processing disorders [16]. A report has indicated a 85.15% probability of alteration of the central auditory processing in individuals with changes in the FFR [17]. Modification of both the latencies and amplitudes of FFR can be found in the population with altered central auditory processing and language deficits; such findings provide crucial information regarding the generation and propagation of responses along the auditory pathway [16].

The difficulty in perceiving consonants is due to their characteristics of fast and transient low-amplitude signal for speech; whereas, the perception of vowels is more resistant because they constitute a periodic, sustained, and generally higher signal than that of the consonants. Perception of the consonant (transient on set) and vowel (sustained) elicit responses through independent mechanisms [9, 18].

Findings caused by central auditory processing disorder, such as delayed latencies and diminished amplitudes, observed in our study, have also been reported in a previous study [19]. Evaluation through speech provides a more sensitive method to investigate the changes in the synchronicity of response generators and extent of neural allocation represented by the amplitude differences, and rate of transmission of neural impulses during processing represented by the latency differences.

A study has shown significantly increased latencies in the V, A, and C waves of the responses in children with learning disabilities [20]. Another report indicated that the latency deficits through FFR have a negative impact on the processing of acoustic signals in specialized cortical structures for speech [16].

With regard to sex, women tend to have earlier absolute latencies and shorter interpeak intervals than men; this difference is associated with the anatomical inequality of the skull and brain, and size of the cochlea [13, 21, 22, 23]. In our study, this difference was observed in the sample corresponding to male individuals (44.4%).

The delay in the wave for both the ABR and FFR was more significant in the age group of 12 to 18 years-old. In adolescents, the signs and symptoms of the disease alter performance and learning which leads to backwardness in schooling [23, 24]. At the stage of adolescence, many problems arise due to the transition from pediatric treatment to that of the adult and greater avoidance of disease control; [23] these also include death rates of 78.6% in individuals up to 29 years [24]. A study using advanced neuroradiological techniques has reported the occurrence of complications of the central nervous system in 44% and 49% of patients with SCD. A report has indicated that silent ischemic injury associated with several neurocognitive deficits, such as learning problems, attention deficit, lack of executive abilities, poor activity status, and long-term memory [7].

Few studies have focused on the evaluation of ABR in the population with SCD, and none on that of FFR. Ondzotto et al. emphasized the importance of encouraging regular hearing assessment in this population [25]. Further studies are needed to clarify these findings due to the high variability of those between studies; however, the variability may be unavoidable due to the characteristic of SCD itself. Serjeant reported that different geographic areas as well as genetic and environmental factors influence variability in the population with SCD [23].

The analysis of auditory evoked potentials at the level of the brainstem revealed a change in 88.9% of subjects with click stimuli and 98.1% with speech stimulus.

Our overall findings highlight the need for prevention, diagnosis, and systematic follow-up in individuals with SCD, since hearing loss that is undiagnosed or diagnosed late can cause irreparable damage to speech, biopsychosocial, and emotional development.

In conclusion, the changes of the ABR and FFR may be considered as indicators of the individuals' hearing status. The finding of auditory thresholds within the normal range and otoacoustic emissions helps, but does not guarantee excellent sound transmission through the auditory pathway. A new approach as well as further studies focused on central auditory processing and rehabilitation in this population are required. The combined use of electrophysiological assessments such as FFR and behavioral tests of central auditory processing may have effectiveness to clearly guide the possible communicative difficulties and enable earlier and more accurate diagnosis in this population.

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Chapter 36

THE RELATIONSHIP BETWEEN SELF-REPORTED RESTRICTION IN SOCIAL PARTICIPATION, SELF-REPORTED SATISFACTION/BENEFIT AND THE TIME OF USE OF HEARING AIDS

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ABSTRACT

To correlate the results obtained through questionnaires concerning self-reported restriction in social participation and patient satisfaction/benefit with objective time assessment of device use. This is a descriptive, cross-sectional study sample composed of and elderly and non-elderly adults of both sexes diagnosed with hearing loss and approved as candidates for hearing aid fitting at a university hospital. Subjects answered questionnaires that measure restriction in social participation restriction and user satisfaction/benefit, namely the Hearing Handicap Inventory for Adults (HHIA) for non-elderly adult patients; the Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S), for elderly patients, and the International Outcome Inventory for Hearing Aids (IOI-HA) for both age groups. Average daily usage time of the devices was verified objectively through datalogging. A total of 49 users elderly and non-elderly of both sexes participated in the study. Self-reported hearing aid times of use were compared with those

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measured by datalogging. There was overestimation on the part of patients when reporting hearing aid use, which was verified when compared with software data. There was no significant correlation between questionnaire scores and the datalogged time of use. There was a negative correlation between the HHIE-S and IOI-HA questionnaires, and a positive correlation between the variable of age and the IOI-HA questionnaire, as well as another positive correlation between the variable of sex and the HHIA questionnaire. No relation was found between datalogged time of use and self-reported restriction in social participation or hearing aid user satisfaction/benefit.

Keywords: hearing aids, hearing loss, questionnaires

INTRODUCTION

According to the National Health Survey of 2013, 1.1% of the Brazilian population - approximately 2.27 million people - are hearing impaired, with the South of the country representing the highest proportion of this indicator (1.5%). Research data also reveal that hearing loss is more frequent in the elderly (5.2%) or among people with lower levels of education or an incomplete elementary education. These findings are highly significant when compared to other data on age and education [1]. Hearing impairment causes disturbances in the social life of elderly patients as well as non-elderly adults and is also associated with other symptoms, such as depression, as well as functional and cognitive decline [2]. In relation to the elderly, it has been shown that hearing loss frequently entails a restriction in social participation and a lack of communicative competence; that is to say, it has a significant impact on the subjects' quality of life [3].

In the Brazilian Unified Health System (SUS), the cost-free fitting of hearing aids (HAs) has been granted since 2000. Public provision policies were amplified after the implementation of the Hearing Care Network for the Hearing Impaired and preceded the elaboration of the National Attention to Hearing Health policy. Since the implementation of these public protocols, demands for promotion, prevention and rehabilitation have been better met at federal, state and municipal levels [4, 5].

In order to facilitate a satisfactory hearing aid adaptation process, a speech-language pathologist qualified in audiology should carry out an appropriate HA selection and then give detailed and careful advice to the patient [6]. After fitting, successful adaptation also depends on the daily time of the use of the HA. This can be accurately measured through datalogging, a feature present in sound amplification devices. In order to validate success or setbacks in the adjustment process, the speech-language pathologist uses questionnaires to subjectively gauge patient satisfaction and benefit from hearing aid use [6]. In scientific literature, studies have been found that describe the importance of measuring user satisfaction/benefit in the process of adaptation. However, few studies correlate datalogged daily time of use with questionnaires that aim at validating the adaptation process.

It is known that the process of selecting and adapting to hearing aids aims to, among other goals, circumvent restrictions in social participation and help the user to effectively make use of their devices, thus favoring user satisfaction/benefit. In this sense, for a well-structured process of verification and validation, orientation, adaptation and self-assessment, questionnaires should be used in the best way possible [7].

Among the questionnaires used to evaluate patient hearing loss are the Hearing Handicap Inventory for Adults (HHIA) and the Hearing Handicap Inventory for the Elderly - Screening Version (HHIE-S) [8]. The first is used to verify participation restriction caused by hearing loss in non-elderly adults and the second is used to verify the same phenomenon in the elderly. Participation restriction or handicap is considered to be any disadvantage imposed by hearing impairment which limits an individual psychosocially. Many times elderly and non-elderly patients with hearing losses need to use hearing aids in order to compensate for the reported deficits caused by hypoacusia. Although these devices are used as a way to address negative social impacts, some accompanying strategies are even more decisive for their successful use, such as the elaboration of realistic expectations together with the patient regarding the compensation provided by the hearing aid. Moreover, appropriate advice and orientation by the speech-language pathologist directly supports patient adjustment, which in turn results in increased perception of satisfaction/benefit and a reduction in handicap [9].

Another necessary task for a speech and language pathologist who works with the selection and adaptation of HAs is to analyze self-reported user satisfaction and benefit. With this objective, after a minimal period of fifteen days post-fitting, the internationally used *Outcome Inventory for Hearing Aids* (IOI-HA) [10] can be applied to verify adjustment to the HA from the user's point of view. It takes into account daily evolution, degree of user satisfaction, impact on other people, restriction in social participation and limitations in basic activities. In addition, the IOI-HA questionnaire allows the patient to report the daily time of use of the hearing aid [11].

In peer-reviewed literature, there are few studies that correlate datalogging to the protocols mentioned previously, with the exception of the IOI-HA protocol. Some studies have found a significant correlation between the time of use of the hearing aid registered through datalogging and the self-reports of users, as well as a correlation between the time of use registered by datalogging with other protocols that measure patient satisfaction/benefit [12, 13]. Thus, the present study has as a general objective the correlation of findings regarding restrictions in social participation caused by the hearing loss, hearing aid user satisfaction/ benefit and the datalogged times of use of these devices. Furthermore, our specific objectives are to analyze the relationship between the questionnaires themselves; to correlate the datalogged time of use and questionnaires with different variables such as age, education and type and degree of hearing loss. What is more, we aim to analyze the correlation between self-reported daily time of use and the datalogged time of use of these devices.

METHODS

The study was of the transversal and descriptive type. The sample consisted of elderly and non-elderly patients of both sexes who had been diagnosed with hearing loss by an Ear, Nose and Throat (ENT) specialist had gone through an audiological evaluation. These subjects were approved as candidates for hearing aid fitting and subsequently received these devices through the National Hearing Health Program at a university hospital.

Inclusion criteria were that recruited patients should sign an Informed Consent form (IC) and have undergone an ENT and audiological evaluation (pure tone audiometry, speech

audiometry and acoustic impedance tests measures). Subjects who received their hearing aids via the program should have been using their devices for at least 15 days. Users under the age of 18 were excluded from the sample as well as patients who demonstrated partial or total incomprehension of the questionnaires due to cognitive, neurological or language issues.

In the process of selection and adaptation of the hearing aids, initial evaluations were carried out to verify the type and degree of hearing loss, along with the most appropriate type of device for each patient's needs. After fitting, patients received individual guidance on the proper use, handling and care of the devices. It should be noted that patients were not informed about the possibility of checking the time of use through datalogging.

After a minimal period of fifteen days, patients returned for a follow-up appointment. This period is a guideline at the outpatient clinic where the research was done. At that time, adjustments, verifications and further explanations about patients' hearing aids were performed, with the aim of guaranteeing continuity of use. Patients were also invited to participate in the research project. After signing the IC form, subjects were shown to a specific room in the outpatient clinic to answer questionnaires. At this stage, only the interviewer and the HA user were present in the interview room, in order to avoid interference from family members and caregivers.

First, subjects answered questionnaires regarding social participation restriction due to hearing loss: the HHIE-S questionnaire for elderly patients or the HHIA for non-elderly adult subjects. Next, the IOI-HA questionnaire was applied to assess user satisfaction/benefit. After, the datalogged daily time of use was verified for the subsequent analysis and correlation of the questionnaire scores and self-reported average daily time of use.

Questionnaires were applied during one-on-one interviews which were adjusted according to the level of education of each research participant. The differences between first two questionnaires, the HHIES-S and HHIA, lie in their distinct target populations as well as the overall number of questions. The former is a shorter version, containing ten questions, five of which address emotional aspects and the other five social/situational aspects. As such, the cut-off points that determine user participation are different than those of the HHIA, which is a questionnaire composed of twenty-five questions. As for the score, four points, two points and zero points were given for the answers "yes", "maybe" and "no", respectively. In both cases, the higher the score, the greater the self-reported restriction in social participation. The HHIE-S questionnaire has a total score of forty points: zero to eight points represents no perceived restriction in social participation, ten to twenty-three a mild to moderate restriction and twenty-four to forty a significant restriction. The HHIA questionnaire has a total score of 100 points: a score of zero to sixteen is indicative of no perceived restriction in social participation, eighteen to thirty points indicate slight restriction, thirty-two to forty points indicate moderate restriction and scores above forty-two points indicate a significant restriction in social participation [14].

The IOI-HA questionnaire was also applied during the interview. This particular instrument should be used within the first 15 days after hearing aid fitting. The questions take into account degree of user satisfaction/benefit, restrictions in social participation and limitations in basic activities [7]. It consists of seven questions, each worth a score of between one to five, where one represents the most negative response and five the most positive. The maximum score is thirty-five points, which is indicative of a very positive evaluation by the HA user, whereas the minimum score of five points is indicative of a negative evaluation by the HA user.

After the application of the questionnaires, an objective verification of time of use was carried out through the datalogging feature, which is present in all HAs distributed at the outpatient clinic. Data regarding sex, age and type and degree of hearing loss were also obtained through patients' electronic records.

The sample size calculation was performed in the WinPEPI program (*Programs for Epidemiologists for Windows*) version 11.43 [12, 13]. For a level of significance of 5%, to the power of 80%, and estimating a minimum correlation coefficient of 0.4 between the variables of satisfaction, benefit and restriction in social participation and time of use, a minimum total of 47 patients was obtained.

Quantitative variables were described by mean and standard deviation or interquartile range and median. Categorical variables were described by absolute and relative frequencies. To compare means between ears, the *t-student* test for paired samples was applied. In cases of asymmetry, the *Wilcoxon* test was used. For the categorical variables, the *McNemar* test was applied. To compare means between gender and type of loss, the *t-student* test for independent samples or Analysis of Variance (ANOVA) were applied. In cases of asymmetry, the *Mann-Whitney* and *Kruskal-Wallis* tests were used. To evaluate the association between continuous and ordinal variables, the *Pearson* or *Spearman* correlation tests were applied. The significance level adopted was 5% ($p \leq 0.05$) and the analyses were performed through the SPSS program, version 21.0.

The present study was submitted to and approved by the Research Ethics Committee (CEP) of the institution, and approved (protocol number 2.086.280). Was regulated according to the norms concerning research involving human beings, duly governed by resolution 466/12 of the National Health Council.

RESULT

The present study consisted of a sample of 49 subjects, the majority of whom were elderly patients (71.42%). Among study subjects, there was equal distribution with regard to sex. Most of the participants in the sample had lower levels of education. The greater part of the group was fitted bilaterally with hearing aids (Table 1).

The HHIE-S questionnaire for the elderly presented a median of 6 and, for non-elderly adults, the HHIA median was 0. Thus, most of the study subjects, both elderly and non-elderly adults, declared no restriction in social participation after the use of HAs. The quantitative data collected through the IOI-HA questionnaire revealed an average score of 29.3 points, which is a good indication of HA user satisfaction/benefit (Table 1).

Regarding the type of hearing loss, the predominant profile was sensorineural, symmetrical, bilateral loss. The most frequent degree of bilateral loss was moderate, based on the quadratic mean (500Hz, 1000Hz, 2000Hz and 4000Hz). The mean post-fitting period until follow up was one month and three days. The average datalogged time of use is presented in Table 2.

Table 1. Characterization of the sample

Variables	n = 49 (35 elderly users and 14 non-elderly adult users)
Age (years) – average $\pm$ SD	66.0 $\pm$ 14.2
Minimum age/maximum age	24/91
Sex – n (%)	
Female	24(49.0)
Male	25(51.0)
Education (years) – median (P25 – P75)	6 (4 – 8)
Hearing aid use – n (%)	
Unilateral	8 (16.3)
Bilateral	41(83.7)
Period of adjustment to HA – average $\pm$ SD	33.6 $\pm$ 3.0
HHIE – S – median (P25 – P75)	6 (0 -10)
HHIE Classification– S – n (%)	
No participation restriction	24(68.6)
Slight to moderate participation restriction	9 (25.7)
Significant participation restriction	2(5.7)
HHIA – median (P25 – P75)	0 (0 - 15.5)
HHIA Classification– n (%)	
No participation restriction	11(78.6)
Slight participation restriction	1(7.1)
Moderate participation restriction	0(0.0)
Significant participation restriction	2 (14.3)
IOI-HA – average $\pm$ SD	29.3 $\pm$ 5.8

Legend: SD – standard deviation; % - percentage; HHIE – Hearing Handicap Inventory for Elderly-S – Screening version; HHIA – Hearing Handicap Inventory for Adult; IOI-HA = International Outcome Inventory for Hearing Aid; HA – Hearing Aids.

Table 2. Patient hearing data and hearing aid time of use registered by datalogging

Variables	Right ear	Left ear	p
	(n = 48)	(n = 46)	
Time of use in hours/day	3 (2 – 7)	3 (1 – 7)	0.380
median (P25 – P75)			
Type of hearing loss – n (%)			0.513
Sensorineural	36(78.3)	36(80.0)	
Conductive	2(4.3)	3(6.7)	
Mixed	8 (17.4)	6 (13.3)	
Degree of hearing loss – n (%)			0.214
High-frequency hearing loss	2(4.2)	1(2.2)	
Mild	16(33.3)	15(32.6)	
Moderate	28(58.3)	23(50.0)	
Severe	2(4.2)	5 (10.9)	
Profound	0(0.0)	2(4.3)	
Quadratic mean – mean $\pm$ SD	47.1 $\pm$ 15.4	51.5 $\pm$ 22.7	0.228

Legend: SD – standard deviation; n – absolute number; p – percentage.

There was a significant negative correlation between the scores of the HHIE-S and IOI-HA questionnaires, showing that the greater the self-reported benefit and satisfaction, the lower the perception of restriction in social participation due to hearing loss. There was no

significant correlation between the scores of the HHIA and IOI-HA questionnaires, nor was there a correlation between the scores of the questionnaires and the objective measures of HA time of use (Table 3).

Table 3. Datalogged time of use and its relationship with subjective measures of hearing aid use (questionnaires)

Relationships	Correlation coefficient	p
HHIE – S and IOI-HA	- 0.635	< 0.001
HHIE – S and time of use RE	0.107	0.545
HHIE – S and time of use LE	0.145	0.428
HHIA and IOI-HA	- 0.240	0.410
HHIA and time of use RE	- 0.354	0.235
HHIA and time of use LE	- 0.087	0.799
IOI-HA and time of use RE	0.159	0.287
IOI-HA and time of use LE	0.152	0.331

Legend: RE – right ear; LE – left ear; HHIE-S – Hearing Handicap Inventory for Elderly – Screening Version; HHIA – Hearing Handicap Inventory for Adult; IOI-HA = International Outcome Inventory for Hearing Aids.

An analysis of the variables of education, age, quadratic mean and type of hearing loss and the scores from the questionnaires showed that there was no significant correlation between most of them, except for the negative correlation between the age variable and the IOI-HA questionnaire. This would suggest that the older the hearing aid user, the lower the level of self-reported satisfaction/benefit (Table 4). There was also an association between the variable of sex and the HHIA questionnaire ($p = 0.020$), revealing that female subjects declared more restriction in social participation, even after fitting, when compared to the male subjects.

In our analysis, we observed a difference between self-reported time of hearing aid use and the time of use objectively measured by datalogging software (Table 5) ($z = - 4.74$). It should be noted that, for such an analysis, self-reported daily time of use was classified according to the scales used in the IOI-HA questionnaire (i.e., ‘never’, ‘less than 1 h/day’, ‘1 - 4 h/day’, ‘4 - 8 h/day’, ‘8 < h/day’).

Table 4.

Relationships	HHIE – S	HHIA	IOI-HA
Education	$r_s = - 0.060$ ($p = 0.731$)	$r_s = 0.033$ ($p = 0.910$)	$r_s = 0.211$ ($p = 0.146$)
Age	$r_s = 0.265$ ($p = 0.124$)	$r_s = - 0.078$ ($p = 0.792$)	$r = - 0.317$ ($p = 0.026$)
Quadratic mean			
RE	$r_s = 0.159$ ($p = 0.363$)	$r_s = 0.090$ ($p = 0.758$)	$r = - 0.121$ ($p = 0.409$)
LE	$r_s = 0.288$ ($p = 0.094$)	$r_s = 0.237$ ($p = 0.415$)	$r = 0.049$ ($p = 0.736$)
Type of hearing loss			
RE	$r_s = 0.084$ ($p = 0.644$)	$r_s = - 0.101$ ($p = 0.742$)	$r_s = - 0.064$ ($p = 0.667$)
LE	$r_s = 0.237$ ($p = 0.177$)	$r_s = 0.430$ ($p = 0.124$)	$r_s = 0.120$ ($p = 0.428$)

Legend: RE – right ear; LE – left ear; HHIE-S – Hearing Handicap Inventory for Elderly – Screening Version; HHIA – Hearing Handicap Inventory for Adult; IOI-HA = International Outcome Inventory for Hearing Aids.

Table 5. Analysis of self-reported HA time of use and its relationship with datalogged time of use

	Never n (%)	Less than 1h/day n (%)	1 – 4 h/day n (%)	4 – 8 h/day n (%)	< 8h/day n (%)	Total n (%)
Never n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Less than 1h/day n (%)	1 (2.05)	0 (0)	1 (2.05)	0 (0)	0 (0)	2 (4.1)
1 – 4 h/day n (%)	0 (0)	0 (0)	4 (8.2)	0 (0)	0 (0)	4 (8.2)
4 – 8 h/day n (%)	1 (2.05)	2 (4.1)	10 (20.4)	4 (8.2)	0 (0)	17 (34.7)
< 8h/day n (%)	0 (0)	1 (2.05)	12 (24.5)	2 (4.1)	11 (22.4)	26 (53.1)
Total n (%)	2 (4.1)	3 (6.15)	27 (55.1)	6 (12.2)	11 (22.4)	49 (100)

In our analysis of education and hearing aid time of use, no relevant association was found, either for the right ear ($r_s = 0.221$ and $= 0.135$) or for the left ear ($r_s = 0.241$ and $= 0.120$). No association between age and time of use was observed, either for the RE ($r_s = 0.174 - 0.202$ p) or for the LE ($r_s = - 0.213 = p 0.170$).

DISCUSSION

Population aging is currently one of the predominant themes in different fields, in Brazil and around the world. Senescence brings about physical changes that justify special health care for this population, which is rapidly changing the morphology of the Brazilian age pyramid [15, 16]. This fact would explain the large number of elderly patients in the present study sample, a reality which can also be corroborated by previously mentioned data concerning hearing loss. In that national health survey, the southern region of Brazil scored higher numbers of hearing loss handicap. Moreover, within this particular group, elderly adults constitute a higher proportion when compared with non-elderly adults [1].

On the other hand, the balance in patient sex observed in our study does not support findings in scientific literature that describe a greater demand for health care by female subjects [17]. The balance in the sample may be justified by the higher prevalence of men over 60 diagnosed with hearing loss, which has also been described in scientific literature [18].

Most of the sample consisted of subjects with lower levels of education or with an incomplete elementary education. This was expected due to the general social profile of the population attended at the university hospital [19]. This common factor among almost all sample participants prevented further analysis due to the homogeneous characteristic of this variable.

A predominant part of the subjects in our sample presented bilateral hearing loss, with the most prevalent type being sensorineural moderate loss. No significant difference between ears was observed. These data confirm those described in specialized literature [20]. During the fitting process, hearing aids were adapted in accordance with the characteristics of hearing loss presented by each patient in the sample. Most were fitted bilaterally, which benefits patients with hearing loss since it better facilitates sound localization and binaural summation, as well as better speech recognition in noisy environments [21].

We found no significant correlation between the results of the questionnaires used in the present study and the variables of schooling, age, quadratic mean and type of hearing loss, with the exception of the relationship between the IOI-HA questionnaire and the variable of age. This further substantiates findings in scientific literature that the older the HA user, the weaker the perception of satisfaction/benefit, since elderly individuals tend to understand age as a reason for disabilities. This general attitude might, therefore, make elderly HA users more demanding in terms of the satisfaction/benefit they expect from hearing aids [9].

Scores from questionnaires that measured self-reported restrictions in social participation or patient satisfaction/benefit in the post-fitting period were similar to those already found in specialized literature [9]. These results justify the negative correlation between the HHIE-S and the IOI-HA questionnaires. There was a significant correlation between the HHIA questionnaire and the variable of sex. Among non-elderly adults, follow-up self-reports revealed a greater perception of restriction in social participation. This may be explained by a stronger concern on the part of the adult female subjects for health issues, which may have influenced the results [17].

The non-association between questionnaire scores and datalogged time of use may be explained by the low average HA use by participants. This data may point to the need for closer and more frequent follow-ups for new users, in order to adjust and verify the adaptation process; two steps which have been referred to in the literature as important for better patient habituation to hearing aids [15]. It is important to note that, even with an average of three hours per day in the first month of adaptation, the subjects in this study predominantly reported benefit and satisfaction with their HAs. What is more, reports regarding restriction in social participation were mostly absent, both in elderly and non-elderly adults. This finding is also similar to those present in scientific literature [11]. It should be taken into account, however, that results may also have been influenced by the fact that these patients received their hearing aids through the unified public health system, at no financial cost to themselves.

The present study showed that sample subjects overestimated the average daily time of use of the hearing aids in their self-report. This finding corroborates previous research [22], in which there was also overestimation in the self-reported time of use of hearing devices; however, the study group was smaller than the sample in this study. It is worth noting that data may reflect certain characteristics of the each sample, since in another study no overestimation in self-reports of sample subjects was observed when compared to the time of use provided by datalogging [13].

It is important to highlight that our study was carried out with participants whose health evaluations and care are provided by a unified public health system. This fact, in turn, probably influenced results with respect to patient perception of time of use, satisfaction/benefit and restriction in social participation. Apart from this, lower levels of education may have compromised patient understanding of the need for hearing aids, as well as instructions regarding the proper handling and care of these devices. In like manner, the overestimated time of use in self-reports may correspond to certain characteristics of particular groups of users who may feel the need to declare increased times because of the way in which the hearing aids are distributed to the public.

Thus, our data show, above all, the need for improved guidance for patients attended at the hospital, taking into consideration the way in which hearing aids are made available to them (for example, via public funds), the need for continued use so that greater and better

benefits can be obtained, as well as the relation between hearing and different aspects of daily life, especially social and cognitive ones.

CONCLUSION

Through questionnaires applied to the patient sample of the present study, we were able to verify that the majority of and elderly and non-elderly users fitted with hearing aids felt satisfied and considered the devices beneficial. Additionally, for the most part, responses revealed no significant restriction in social participation. However, no association was found between the questionnaires and the datalogged times of use. Nonetheless, there was a significant difference between question one of the IOI-HA questionnaire and datalogged times of use, suggesting an overestimation in the self-reported time of use of hearing aids by patients. There was a negative correlation between the HHIE-S and IOI-HA questionnaires. This brings to the fore the important relationship between patients self-reporting no restriction in social participation as well as satisfaction and benefit after being fitted with hearing aids.

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VOLUME 3

Chapter 37

**TELECOMMUNICATIONS RELAY SERVICE:
FCC SHOULD STRENGTHEN ITS MANAGEMENT OF
PROGRAM TO ASSIST PERSONS WITH HEARING OR
SPEECH DISABILITIES***

United States Government Accountability Office

WHY GAO DID THIS STUDY

TRS allows persons with hearing or speech disabilities to place and receive telephone calls, often with the help of a communications assistant who acts as a translator or facilitator between the two parties having the conversation. FCC is the steward of the TRS program and the federal TRS Fund, which reimburses TRS providers.

GAO was asked to examine FCC's management of the TRS program. This report examines, among other things, (1) changes in TRS services and costs since 2002, (2) FCC's TRS performance goals and measures and how they compare with key characteristics of successful performance goals and measures, and (3) the extent to which the design of the program's internal control system identifies and considers program risks. GAO analyzed 2002 through 2014 service and cost data, compared TRS performance goals and measures to key characteristics of successful performance goals and measures, compared the design of the TRS's internal control system with GAO's standards for internal control, and interviewed officials from FCC, the 10 companies providing interstate TRS, and associations representing the deaf and hard of hearing.

* This is an edited, reformatted and augmented version of a United States Government Accountability Office publication, No. GAO-15-409, dated April 2015.

WHAT GAO RECOMMENDS

GAO recommends that FCC develop specific TRS performance goals and measures, conduct a robust program risk assessment, and improve the communication of TRS's rules and procedures. In commenting on a draft of this report, FCC agreed with the recommendations and discussed actions it plans to take to implement them.

WHAT GAO FOUND

Since 2002, the overall minutes of use and costs for the Telecommunications Relay Service (TRS) program have grown significantly due to the advent of Internet-based forms of TRS and increased usage by the deaf and hard-of-hearing communities. Program data show that total TRS minutes have grown from about 53 million in “rate year” (July-to-June) 2002–2003 to about 249 million in rate year 2013–2014, an almost five-fold increase. Total TRS costs have grown from about \$104 million in the 2002–2003 rate year to about \$818 million in the 2013–2014 rate year, an almost eight-fold increase. These increases stem from the popularity of new forms of TRS that use the Internet—such as Video Relay Service (VRS) and Internet Protocol Captioned Telephone Service—and the growth in consumers’ use of them, according to FCC, some providers, and one consumer group that GAO interviewed.

The purpose of the TRS program under federal law is to provide persons who are deaf or hard of hearing or have a speech disability with telecommunications services that are “functionally equivalent” to those provided to persons without a hearing or speech disability, but FCC has not established specific performance goals to guide its efforts. FCC has established some performance measures for TRS in the form of minimum performance standards for TRS providers, such as regulations requiring that TRS communications assistants must answer 85 percent of TRS calls (except VRS) within 10 seconds; however, these standards are not linked to higher-level performance goals. By establishing performance measures before establishing performance goals, FCC may be spending time and resources on efforts not well linked to key dimensions of the program. Because of the lack of specific TRS performance goals—and specific performance measures crafted around those goals—it is difficult to determine in an objective, quantifiable way if TRS is making available functionally equivalent telecommunications services, and it is difficult for FCC to manage the program in a proactive, results-oriented manner.

FCC has designed some internal controls for the TRS program, but lacks a comprehensive internal-control system to manage program risks. To address fraud, FCC has designed numerous controls to address compliance risks. For example, FCC eliminated the ability of TRS providers to use subcontractors in 2011 and strengthened TRS's provider-certification rules and user registration rules in 2013. Internal control standards call for the completion of a risk assessment to identify and analyze program risks. FCC's last risk assessment, in 2013, was a one-page document that did not comprehensively identify programmatic risks. A robust risk assessment would help FCC identify risks to providing functionally equivalent services and inform the development of the overall internal-control system. Internal control standards also call for effective external communications to groups that can impact the program, such as TRS's users and providers. FCC's program policies are

spread across numerous reports and orders. Six of 10 TRS providers told us they experienced difficulties understanding TRS rules. FCC has sought comment on how best to reorganize its rules to improve clarity, but has not yet adopted any such changes. Doing so could improve FCC’s communication of TRS rules and procedures to the deaf community and the companies providing services.

ABBREVIATIONS

ADA	Americans with Disabilities Act of 1990
ASL	American Sign Language
CA	“communications assistant”
CTS	Captioned Telephone Service
FCC	Federal Communications Commission
FMFIA	Federal Managers’ Financial Integrity Act of 1982
GPRAMA	GPRA Modernization Act of 2010
HHI	Herfindahl-Hirschman Index
IP CTS	Internet Protocol Captioned Telephone Service
IP Relay	Internet Protocol Relay
NAD	National Association of the Deaf
NECA	National Exchange Carrier Association
MARS	Multi-state Average Rate Structure
OIG	Office of Inspector General
RLSA	Rolka Loube Saltzer Associates
STS	Speech-to-Speech Relay Service
TRS	Telecommunications Relay Service
TTY	Text Telephone
VRS	Video Relay Service

* * *

April 29, 2015

The Honorable Jeff Sessions
United States Senate

Dear Senator Sessions:

Persons with hearing or speech disabilities want or need to have telephone conversations with persons who do not have such a disability— for example, a call to their doctor, their child’s school, or a close relative. The Telecommunications Relay Service (TRS) allows persons with a hearing or speech disability to place and receive telephone calls with the help of a “communications assistant,” (CA) who acts in various ways as an interpreter or facilitator between the two parties having the conversation.¹ Different forms of TRS involve different technologies, including the use of video, the Internet, or special caption telephones. Section

401(a) of the Americans with Disabilities Act of 1990 (ADA)² requires the Federal Communications Commission (FCC), the steward of the TRS program and the Interstate Telecommunications Relay Services Fund (TRS Fund),³ to ensure that TRS is available, to the extent possible and in the most efficient manner, to persons in the United States with hearing or speech disabilities.⁴ TRS Fund disbursements were approximately \$818 million in the 2013–2014 “rate year,”⁵ up from about \$104 million in the 2002–2003 rate year, when according to FCC, Video Relay Service (VRS)—a popular form of TRS—began to be widely offered.⁶

In 2008, the FCC Office of Inspector General (OIG) initiated an investigation into VRS fraud. Several individuals eventually pleaded guilty to committing VRS fraud, and FCC made changes to program rules intended to prevent and detect fraud, waste, or abuse in the program. You requested that we examine FCC’s management of the TRS program.⁷ This report addresses the following questions:

- 1) How have the services and costs of the TRS program changed since 2002?
- 2) What are FCC’s performance goals and measures for the TRS program, and how do they compare with key characteristics of successful performance goals and measures?
- 3) To what extent does the design of the TRS program’s internal control system identify and consider program risks?
- 4) According to program stakeholders, what challenges, if any, exist in ensuring quality services for users and a competitive environment for providers?

For each of our research questions, we reviewed relevant FCC TRS orders and comments filed in FCC proceedings. We also conducted interviews with officials from the FCC; the FCC Office of Inspector General (OIG); Rolka Loube Saltzer Associates (RLSA), the current TRS Fund administrator; the National Exchange Carrier Association (NECA), the previous TRS Fund administrator; each of the 10 companies currently providing TRS; and associations representing the deaf, hard of hearing, and speech-disabled (referred to in this report as consumer groups). We analyzed these interviews to identify major themes that emerged about how and why TRS services have changed over time and what issues exist regarding quality, competition, and management of the program. To determine how the services and costs of the TRS program have changed since 2002, we obtained and analyzed FCC program data on costs and minutes of usage from 2002 through 2014 for the six major TRS services. We selected 2002 as the start date for our review because it was the first year that VRS—the service that accounts for the majority of TRS Fund payments—was widely offered. Based on documentation and conversations with FCC about how the data are collected and managed, we determined the cost and usage data were sufficiently reliable for the purposes of presenting program trends. To assess FCC’s performance goals and measures, we reviewed FCC documents, including strategic plans and performance plans, and interviewed FCC staff about the program’s goals and measures. We compared the goals and measures to key characteristics of successful goals and measures, as developed by GAO in previous work⁸ and as contained in the GPRA Modernization Act of 2010 (GPRAMA).⁹ To assess how the design of the TRS program’s internal control system identifies and considers program risk, we obtained TRS’s internal control documentation, including risk assessments, descriptions of control activities, and audit reports. We compared the design of the TRS internal control

system with the requirements contained in GAO's *Standards for Internal Control in the Federal Government*.¹⁰ To obtain quantifiable information about issues related to TRS quality and competition, we conducted a survey of all 10 current TRS providers. We obtained a 100-percent response rate to our survey. In addition, we conducted a market concentration analysis of the six main forms of TRS by analyzing the number of providers for each service from 2008 through 2014.¹¹ We also analyzed other measures of market concentration for the two largest forms of TRS (VRS and Internet Protocol Captioned Telephone Service) in terms of current compensation received by providers for the most recent rate years. Appendix I provides additional information about our objectives, scope, and methodology, including a list of the organizations we interviewed.

We conducted this performance audit from April 2014 to April 2015, in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

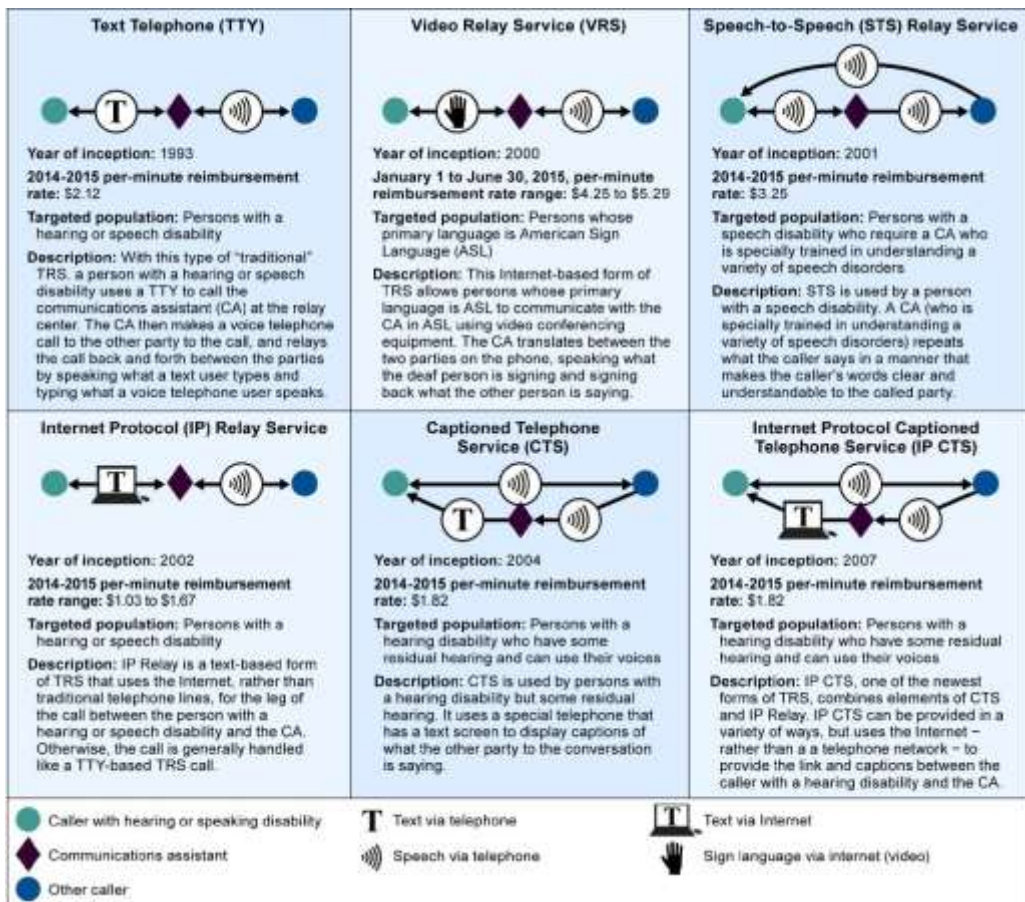
BACKGROUND

FCC manages and oversees the federal TRS program. FCC develops program rules and policies, sets annual rates for compensating providers, and oversees compliance with program rules. FCC contracts out the daily administration of the TRS Fund to a third-party administrator. NECA was the fund administrator from 1993 through June 2011; RLSA has been the administrator since July 2011. The administrator calculates proposed TRS compensation rates and contribution factors, collects fees, and handles the disbursements from the TRS Fund to TRS providers.

According to FCC officials, prior to the ADA, there was no federal requirement for telephone providers to offer a means for people who were deaf, hard of hearing, or speech disabled to access the nation's telephone services, although many states provided a form of TRS at that time. The ADA created the first requirement for a federal program, and the TRS program was established in 1993 in response. The ADA requires that persons with hearing or speech disabilities be provided with telecommunications services that are "functionally equivalent" to the services provided to persons without hearing or speech disabilities.¹² Until 2000, text-to-voice communication using a text telephone (TTY), a text input device, was the only form of TRS available to users. The advent of Internet-based TRS technologies, however, has increased telecommunications options for people who are deaf and hard of hearing. TRS is available in all 50 states, the District of Columbia, and the U.S. territories for local and long distance calls and some international calls. TRS involves no additional charges for the TRS user.¹³ According to FCC officials, FCC has plans to develop a central user-registration database, but currently the number of TRS users is unknown. FCC officials told us that there are roughly 250,000 assigned VRS numbers, but assigned numbers do not equate one-to-one with the number of users.¹⁴ The Centers for Disease Control and Prevention's National Center for Health Statistics reported in February 2014 that there are about 38-million individuals with hearing disabilities in the United States. Although the number of current

TRS users is likely much lower than that, according to the National Association of the Deaf, this number could represent the number of potential users.

There are currently six main forms of TRS: Video Relay Service (VRS), Text Telephone (TTY), Captioned Telephone Service (CTS), Internet Protocol Captioned Telephone Service (IP CTS), Internet Protocol Relay (IP Relay), and Speech-to-Speech Relay Service (STS) (see fig. 1).



Source: GAO analysis of FCC data. | GAO-15-409.

Note: In December 2014, FCC's Consumer and Governmental Affairs Bureau adopted a mid-year adjustment of the IP Relay rate for the sole provider remaining in this market. The rate is currently set at \$1.37 for the first 300,000 minutes through June 30, 2015, and \$1.67 for minutes over 300,000 until May 31, 2015. This adjustment was made because the remaining provider asserted that it would be unable to remain in this business without such rate increases and FCC was concerned that ending this service would harm consumers.

Figure 1. Description of the Six Forms of Telecommunications Relay Service (TRS) (as of January 1, 2015).

TRS providers include both traditional telecommunications companies, such as AT&T or Sprint, and companies primarily focused on providing TRS service, such as Convo or the Communication Axxess Ability Group. Companies are compensated from state TRS funds for the costs of providing intrastate TRS and from the federal TRS Fund for the costs of

providing interstate and Internet-based TRS. There are currently 10 TRS providers that are compensated from the federal TRS Fund. No single company offers all six forms of TRS. For example, in October 2014, six companies provided VRS, while three provided TTY and CTS. For all forms of Internet-based TRS, providers must be certified by FCC before they can offer service.

TRS companies provide TRS services and are then reimbursed on a per-minute basis out of the TRS Fund.¹⁵ The TRS reimbursement rate varies by service and is typically set by FCC annually based on reported provider costs, which include an 11.25-percent return on capital investment. For example, as shown in figure 1, the 2014–2015 reimbursement rates ranged from \$1.03 per minute to \$5.29 per minute for the different forms of TRS. In the 2013–2014 rate year, approximately \$818 million in total reimbursements were paid out of the TRS Fund to the companies that provided TRS services.

The rates for the various forms of TRS are determined in the following ways:¹⁶

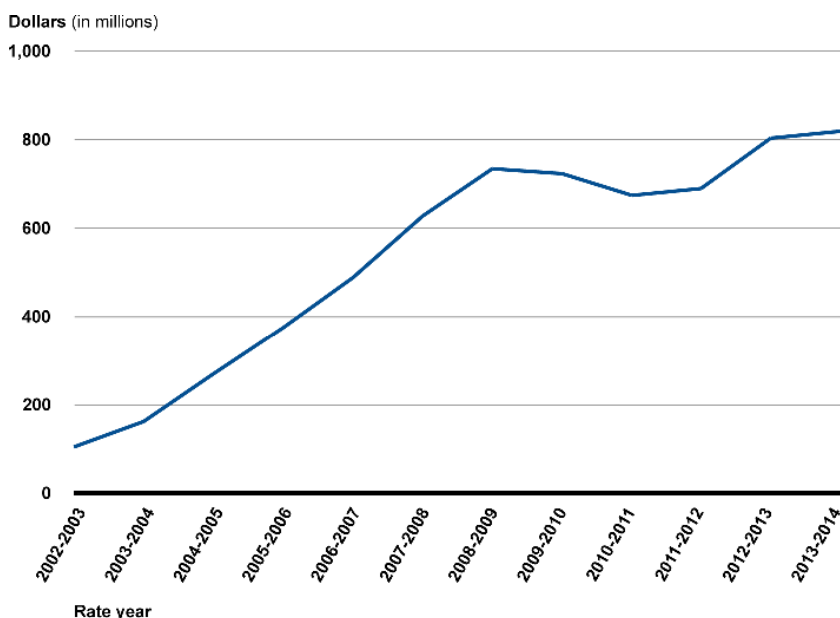
- **Text Telephone, Speech-to-Speech, Captioned Telephone Service, and Internet Protocol Captioned Telephone Service:** FCC uses the Multi-state Average Rate Structure (MARS) methodology to determine compensation. MARS uses an average of competitively bid state rates for intrastate TRS to determine predictable, fair, and reasonable costs of interstate TRS.
- **Internet Protocol Relay:** FCC employs a price cap regulation to determine the compensation rate for IP Relay.
- **Video Relay Service:** According to FCC, to encourage competition while recognizing efficiencies through economies of scale, FCC compensates VRS providers using a three-tiered rate structure based on the minutes of service provided. For January 1, 2015, through June 30, 2015, VRS rates are:
 - **Tier I rate:** \$5.29 per minute for minutes up to 500,000 per month;
 - **Tier II rate:** \$4.82 per minute for minutes from 500,000.1 to 1,000,000 per month; and
 - **Tier III rate:** \$4.25 per minute for minutes over 1,000,000 per month.

All VRS providers are compensated at the tier I rate for their first 500,000 minutes, but as providers become larger and provide more minutes of service, they are compensated at lower rates for the additional minutes. The three-tier rate structure is intended to reflect cost differences among large and small providers and encourage current entrants to remain in the VRS market, while improving their efficiency over time. FCC intends to eliminate the rate tiers over time. In its 2013 VRS Reform Order, FCC adopted a schedule to phase out the differences between tier I and tier II rates by January 2016 as part of a “glide path” toward an eventual unitary cost-based rate for VRS.¹⁷ According to FCC, it is seeking to replace the cost-of-service ratemaking approach for VRS with more market-based approaches, to the extent that this approach can be accomplished without adversely affecting the public interest and goals of the ADA. FCC believes that a market-based approach to providing VRS will result in lower costs for the TRS program.

TOTAL TRS MINUTES AND COSTS HAVE GROWN SIGNIFICANTLY SINCE 2002 DUE TO INTERNET-BASED TRS AND INCREASED USAGE

According to officials from FCC, most of the TRS providers, and all of the consumer groups that we interviewed, the development of Internet-based TRS technologies and increased usage of these technologies have led to growth in overall program minutes and costs. TRS program data show that total TRS minutes have grown from about 53 million in rate year 2002–2003 to about 249 million in rate year 2013–2014, an almost fivefold increase. Total TRS costs have grown from about \$104 million in 2002 to about \$818 million in rate year 2013–2014, an almost eight-fold increase (see fig. 2). According to FCC, some providers, and one consumer group we spoke with, the development of TRS technologies that use the Internet—such as VRS, IP Relay, and IP CTS, along with consumer knowledge about them—has led to wider use of TRS services. Since the federal TRS Fund supports the provision of Internet-based TRS, a rise in federal TRS costs occurred in concert with the development and popularity of the Internet-based services (VRS initially and then IP CTS). According to FCC, some providers, and one consumer group, other technology advancements also have increased TRS usage. For example, CTS and IP CTS involve the use of a telephone that provides people who are hard of hearing with captions of what the other party to the conversation is saying. CTS and IP CTS have opened the TRS market to a new group of users—senior citizens—some of whom can become increasingly unable to follow everything said in a telephone conversation due to hearing loss late in life. Also, two consumer groups noted that consumers can now use mobile phone applications to access most TRS, thus no longer being tied to specialized equipment in the home and likely further increasing total program usage.

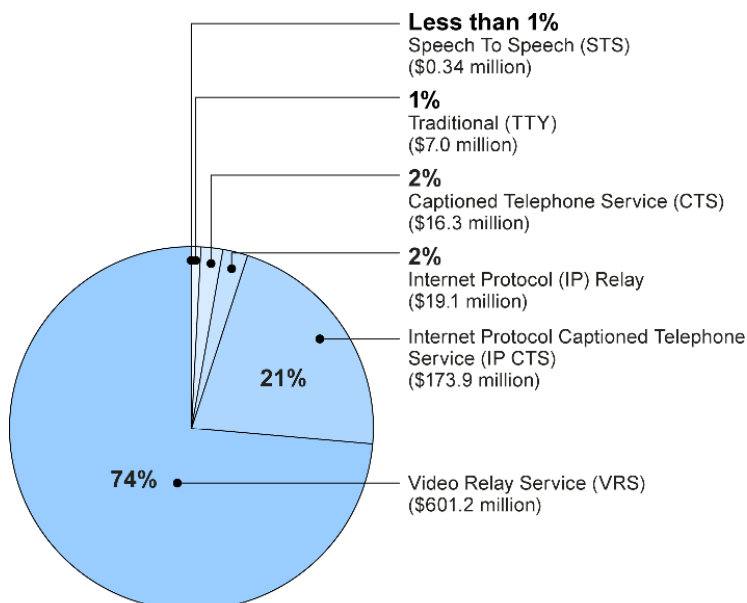
The largest portion of TRS costs are for VRS, which is used by members of the deaf population who communicate in American Sign Language (ASL). According to the National Association of the Deaf (NAD), the primary reason for VRS's increased use is that it allows users to communicate at roughly 200 words-per-minute instead of the 60 words-per-minute enabled by the typing of traditional TTY. In addition, according to NAD, ASL can be a deaf individual's native language and, when used as part of a telephone conversation, provides a richer communication experience, much closer to that of a hearing individual. VRS requires a specialized CA workforce of ASL interpreters who, according to some of the stakeholders we spoke with, can be in low supply and can command fairly high salaries. These higher CA costs and, according to one provider, the more expensive video link between the deaf individual and the CA have led to VRS costs per minute that are higher than other forms of TRS. VRS costs grew from about \$25 million in rate year 2002–2003 to about \$601 million in rate year 2013–2014. VRS reimbursement costs peaked in the 2008–2009 rate year at \$621 million, which accounted for about 85 percent of the TRS fund at that time. In rate year 2013–2014, VRS accounted for about 74 percent of the \$818 million in TRS reimbursements (see fig. 3). IP CTS is the second most reimbursed TRS service at about 21 percent of total TRS costs.



Source: GAO analysis of FCC data. | GAO-15-409.

Note: According to FCC officials, cost data from some TRS forms prior to July 2011 either could not be located or were not reliable, so these data are not part of this graphic. However, these omissions do not significantly affect this graphic because they were low amounts at the beginning of the TRS forms' availability.

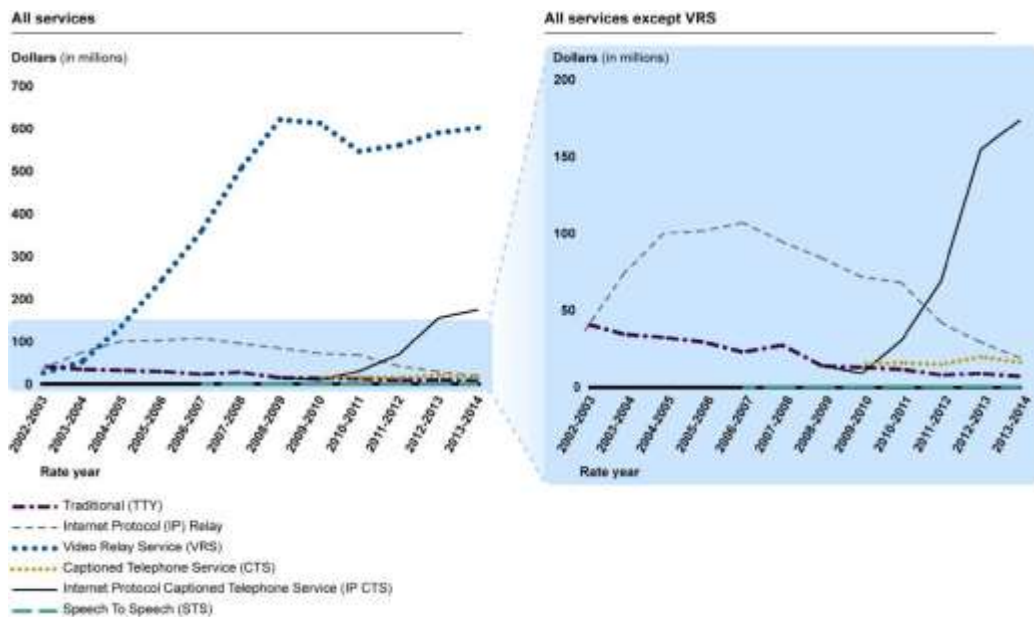
Figure 2. Total Telecommunications Relay Service Program Costs, 2002–2003 to 2013–2014.



Source: GAO analysis of FCC data. | GAO-15-409.

Figure 3. Percentage of Total Costs of Each Form of Telecommunications Relay Service in Rate Year 2013–2014.

Although VRS costs are the largest percentage of current program costs, IP CTS costs are growing at the fastest rate. From rate years 2009–2010 through 2013–2014, IP CTS grew from \$9 million to \$174 million, or about a 19-fold increase (see fig. 4). Some stakeholders we spoke with saw IP CTS as an area where TRS usage is likely to continue increasing as baby boomers age and face increased hearing loss. Today, VRS and IP CTS, both Internet-based technologies, account for about 95 percent of TRS costs.



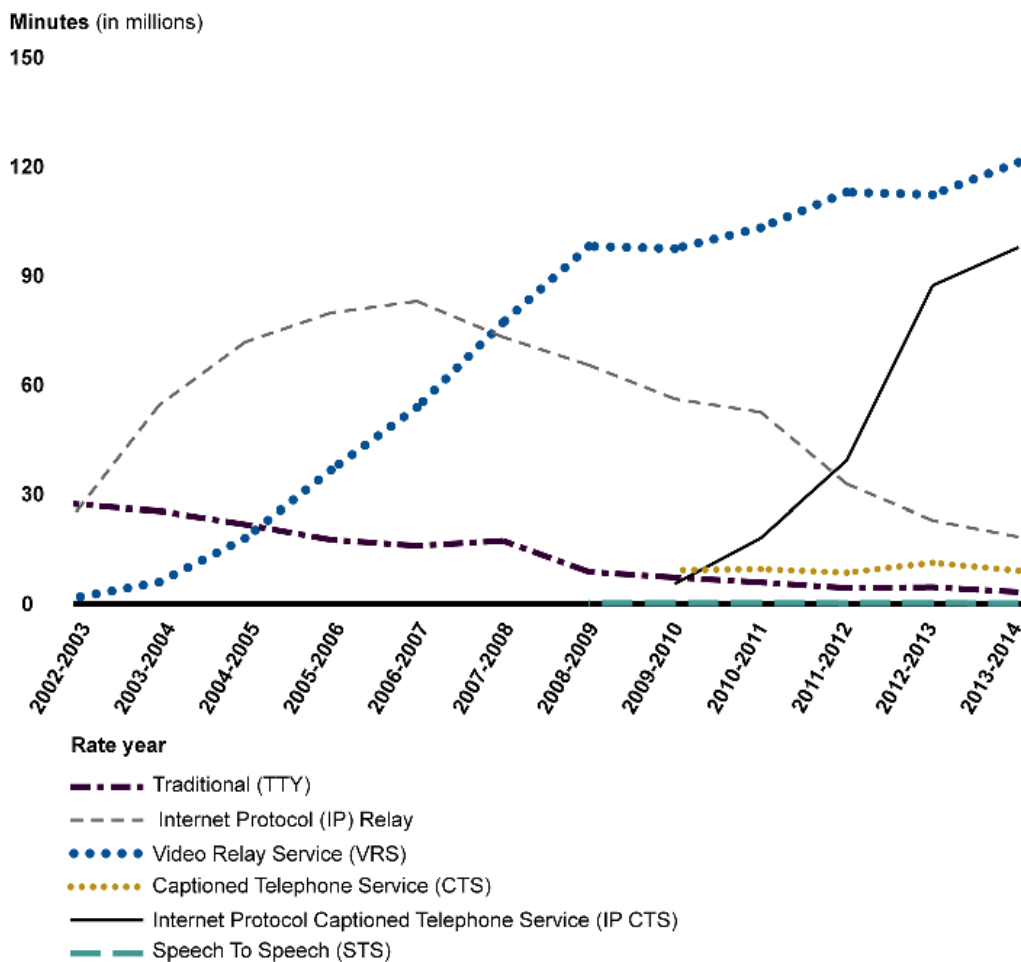
Source: GAO analysis of FCC data. | GAO-15-409.

Note: We did not include cost data for CTS and IP CTS prior to July 2009 in this graphic because, according to FCC officials, it either did not exist or was not reliable. In addition, according to FCC officials, prior to July 2006, STS cost data were combined with TTY cost data.

Figure 4. Total Costs for Each Form of Telecommunications Relay Service, 2002–2003 to 2013–2014.

As shown in figures 4 and 5, other forms of TRS are declining or staying the same in terms of costs and usage. IP Relay and traditional TTY, both of which require the person who is deaf or hard of hearing to type his or her part of the conversation, are declining in both minutes of use and costs. IP Relay minutes have decreased from about 83 million in rate year 2006–2007 to about 18 million in rate year 2013–2014. TTY minutes have decreased from about 27 million in rate year 2002–2003 to about 3 million in rate year 2013–2014. Similarly, total program costs for both services have declined as well. Officials from FCC, TRS providers, and consumer groups told us that the growth in popularity of VRS and IP CTS have contributed to a decrease in the popularity of IP Relay and TTY. VRS and IP CTS allow for much quicker and more natural conversations than the text-based IP Relay and traditional TTY. In recent years, CTS and STS have remained at a steady level in both minutes of use and costs. CTS functions like IP CTS, but uses the traditional telephone network rather than the Internet. STS serves a small, discrete population with severe speech disabilities. As shown in figure 3, both services account for small percentages of the entire cost of the TRS Fund. In rate year 2013–2014, CTS costs accounted for about 2 percent of the fund, while total STS

costs were less than 1 percent of the fund. Figure 5 shows changes in minutes of use from rate years 2002–2003 through 2013–2014 for each form of TRS.

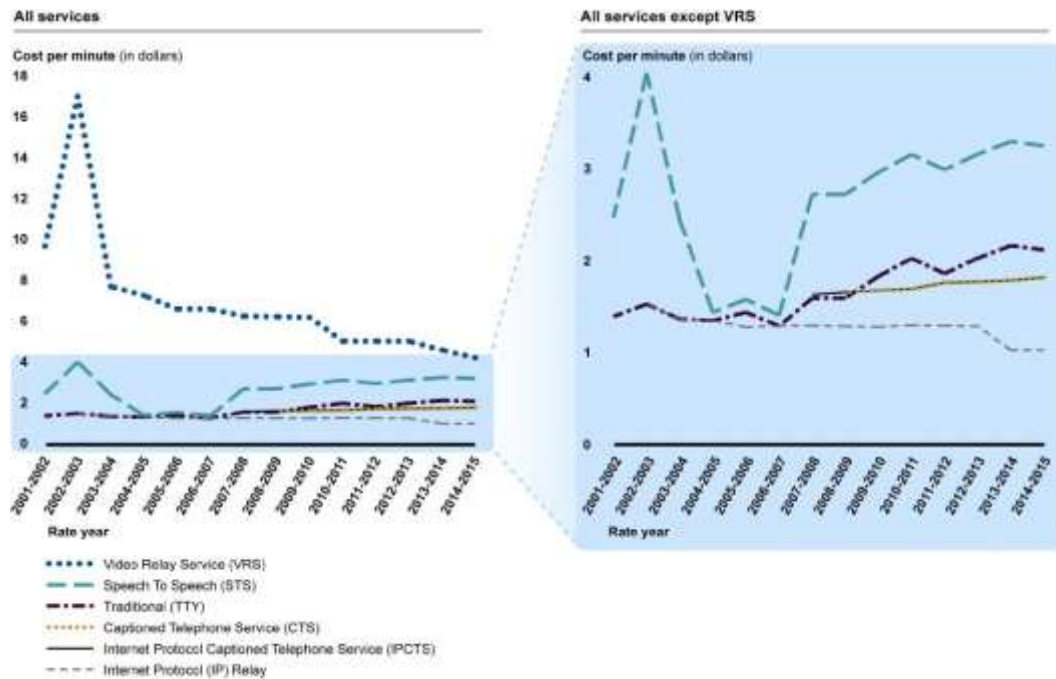


Source: GAO analysis of FCC data. | GAO-15-409.

Note: GAO did not include minutes of usage data for CTS and IP CTS prior to July 2009 because, according to FCC officials, data did not exist or were not reliable.

Figure 5. Changes in Minutes of Use for Each Form of Telecommunications Relay Service, 2002–2003 to 2013–2014.

The per-minute reimbursement rates for TRS have varied over time, although the reimbursement rate for VRS has decreased significantly. VRS reimbursement rates decreased from about \$17 per minute in 2001–2002 to about \$4.25 per minute for VRS Tier 3 in 2015 (see fig. 6). Nonetheless, despite this decrease in the VRS reimbursement rate, its costs have grown significantly over this time period due to increased usage as discussed previously. The reimbursements rates for other forms of TRS, such as CTS, IP CTS, TTY, and STS, have increased moderately since 2011, while rates for IP Relay have decreased.



Source: GAO analysis of FCC data. | GAO-15-409.

Note: GAO used reimbursement rates for VRS tier III from rate year 2007-2008 through rate year 2013-2014. Reimbursement rates for IP Relay begin in rate year 2002-2003. Reimbursement rates for CTS and IP CTS begin in rate year 2007-2008.

Figure 6. Trends in Telecommunications Relay Service (TRS) Cost Reimbursement Rates over Time.

According to FCC, one provider and one consumer group, reducing fraud also has played a role in reducing costs for some forms of TRS. According to the FCC OIG, as the FCC OIG investigated VRS fraud and VRS reimbursement rates decreased, VRS costs decreased from rate year 2008-2009 to rate year 2010-2011, as shown in figure 4, even as VRS minutes increased in these rate years. In addition, FCC officials have told us that the efforts of the FCC Enforcement Bureau and OIG have contributed to a decrease in IP Relay costs. For example, according to FCC officials, FCC's Enforcement Bureau investigated IP Relay providers to determine whether they had implemented a reasonable process to verify the accuracy of users' registration information.¹⁸ Similarly, the FCC OIG worked with the Department of Justice to investigate allegations that a TRS provider had submitted false claims, such as Nigerian scam calls, from foreign locations in provision of an IP Relay.¹⁹ The FCC OIG attributes some of the reductions in IP Relay costs since 2008 to these fraud reduction efforts. In addition to its fraud reduction efforts, FCC made TRS providers' research and development costs and outreach costs no longer reimbursable in FCC's June 2013 VRS Reform Order, which could also reduce costs for some forms of TRS.²⁰

FCC HAS NOT ESTABLISHED PERFORMANCE GOALS AND RELATED PERFORMANCE MEASURES FOR THE TRS PROGRAM

We have previously found that results-oriented organizations commonly perform a number of key practices to effectively manage program performance.²¹ In particular, results-oriented organizations implement two key practices to lay a strong foundation for successful program management. First, these organizations set performance goals to clearly define desired program outcomes. Second, they develop performance measures that are clearly linked to the performance goals.

With regard to the TRS program, the ADA directs FCC to ensure that telecommunications services are available, to the extent possible and in the most efficient manner, to persons with a hearing or speech disability, and that such services are “functionally equivalent” to the telecommunications services available to individuals without a hearing or speech disability.²² All of the FCC officials with whom we spoke agreed that the high-level purpose of the TRS program is this provision of functionally equivalent telecommunications to people with hearing or speech disabilities, but FCC has not established specific performance goals to guide its efforts toward achieving that purpose. Officials told us that they believe that the TRS program’s rules and numerous related reports and orders have sufficiently identified the performance goals of the program. We identified some performance measures associated with the program, but these measures are not clearly linked to any agency or program performance goals and are sometimes not well defined or measurable. Without stated program goals, it can be challenging for FCC to determine the extent to which it is fulfilling the purpose of the program.

The Government Performance and Results Act requires agencies to develop a performance plan covering each program activity set forth in the budget, which includes developing program goals that are objective, quantifiable, and measurable.²³ TRS is mentioned in FCC’s most recent budget request and performance plan, which, for budgetary purposes, groups TRS with FCC’s four universal service support programs. However, there are no stated performance goals specific to the TRS program. There have been performance goals for TRS in previous performance plans. For example, in its fiscal year 2012 performance plan, FCC had a goal to increase access to TRS services. However, this goal does not appear in current performance plans, and FCC officials told us they were unable to determine how many unique users participated in the TRS program or the number of potential TRS users. Thus, no performance measure—or method for obtaining the measurement data—was linked to this goal, making it difficult for FCC to demonstrate whether or to what extent access to services among the target populations had increased.

One useful practice for developing successful performance goals that we have identified in previous work is to create a set of goals that address important dimensions of a program’s performance and balance competing priorities.²⁴ For example, officials told us that important dimensions of the program are, among other things, the quality of the services provided to users and the existence of competition among TRS providers. However, FCC has not established performance goals related to these dimensions. For instance, FCC lacks any goal related to interpreter accuracy, which consumer groups we met with stressed was critical to achieving quality services. Accurate relay of important medical, legal, or financial calls by CAs was of particular concern to consumer groups with whom we spoke. Without goals

related to important dimensions of service quality, such as interpreter accuracy, it becomes difficult to determine if this attribute of functional equivalency is being met and to identify whether programmatic changes need to be made. FCC officials acknowledged that there is no interpreter accuracy goal, but stated that they believe there is no practical way to evaluate interpreter accuracy. However, the consumer groups and some service providers we met with told us that interpreter accuracy could be evaluated with test scripts. Similarly, with regard to the important program dimension of competition, different numbers of providers offer different forms of TRS, but FCC has no performance goals with relation to levels of competition or ratemaking. For example, FCC stated in its 2013 VRS Reform Further Notice of Proposed Rulemaking that it believes there is a need to replace its VRS cost-of-service ratemaking with more market-based approaches, and proposed transitioning to contract prices set through a competitive-bidding process, where feasible, and auctioning a portion of VRS traffic.²⁵ However, the proposed rulemaking set forth a number of questions about how such an approach would work, including questions about bidder qualifications and ensuring the quality of services. Establishing performance goals around competition and ratemaking could help guide FCC's efforts in these areas and improve the transparency of FCC's actions, as decisions could more clearly be linked to the achievement of program goals.

Although FCC lacks specific performance goals, FCC does have in place some specific performance measures for TRS in the form of minimum program standards.²⁶ Compliance with the minimum standards is necessary for providers to receive compensation from the TRS Fund. These performance measures include, among others, that:

- Providers shall transmit traditional TRS conversations in real time.
- CAs must have a typing speed of at least 60 words per minute.
- Providers must have the following service functionalities: (1) call release, (2) speed dialing, and (3) three-way calling.
- Emergency calls must be able to be expeditiously transferred to an emergency services provider as if a caller had dialed 911 directly.
- TRS calls (except VRS) must be answered by CAs within 10 seconds 85 percent of the time.

In addition, to its credit, FCC has formally established performance measures for the TRS Fund administrator. For example, measures such as the timeliness of TRS Fund collections, payments, and status reports to FCC, among others, are included in FCC's contract with RLSA.

Although FCC has established some TRS performance measures, these measures are not linked to any TRS or universal-service performance goals. By establishing performance measures before establishing performance goals, FCC may be spending its time and resources, and those of the service providers or program administrator, on efforts not well linked to key dimensions of the program. Also, the performance measures FCC is using for the program can be difficult to assess because criteria are lacking. For instance, other minimum standards state, among other things, that CAs must be "sufficiently trained" to meet the needs of individuals with hearing and speech disabilities; must have "competent skills" in grammar, spelling, and interpretation of typewritten ASL; and must possess "familiarity" with hearing and speech disability cultures, languages, and etiquette. These terms are not defined by FCC and, as a result, are difficult to measure in a consistent manner across TRS providers.

It is up to the service providers to determine that they are meeting these requirements and self-certify that they are doing so.²⁷

Thus, although FCC has developed some important performance output measures through its minimum standards for the TRS program, best practices for successful management of a program call for a well-balanced set of outcome and output measures that link to specific program performance goals.²⁸ Performance measurement is critical to determining a program's progress in meeting its intended outcomes and allowing Congress, FCC, and RLSA to assess the effectiveness of the TRS program and determine if operational changes are needed. Because of the lack of specific TRS performance goals—and specific performance measures that are crafted around those goals—it is difficult to determine in an objective, quantifiable way if TRS is fulfilling its purpose of making available functionally equivalent telecommunications services to persons with hearing and speech disabilities, and it is difficult for FCC to manage the program in a proactive, results-oriented manner.

FCC HAS DESIGNED SOME INTERNAL CONTROLS BUT LACKS A COMPREHENSIVE INTERNAL CONTROL SYSTEM TO MANAGE PROGRAM RISKS

An Internal Control System Helps Assure That Program Goals Are Met

Internal control is an integral component of an agency's management process that provides reasonable assurance that the objectives of an agency's program are being achieved. Program objectives can be broadly classified into one or more of the following categories:

- **Operations:** the effectiveness and efficiency of program operations;
- **Reporting:** the reliability of reporting for internal and external use; and
- **Compliance:** program compliance with applicable laws and regulations.

GAO's *Standards for Internal Control in the Federal Government* commonly referred to as the "*Green Book*," defines the standards for internal control in the federal government.²⁹ The Federal Managers' Financial Integrity Act of 1982 (FMFIA) requires federal executive-branch entities to establish internal control in accordance with these standards.³⁰ GAO has developed a tool to assist agencies in this process,³¹ as has OMB with its *Circular A-123*.³² The *Green Book* identifies the following five components as being the highest level of the hierarchy of standards for internal control in the federal government:

- **Control Environment:** The foundation for an internal control system. The control environment provides the discipline and structure to help an entity achieve its objectives.
- **Risk Assessment:** Assesses the risks facing the entity as it seeks to achieve its objectives. This assessment provides the basis for developing appropriate risk responses.
- **Control Activities:** The actions management establishes through policies and procedures to achieve objectives and respond to risks in the internal control system.

- **Information and Communication:** The quality of information that management uses to support the internal control system. Communicating quality information is vital for an entity to run and control its operations.
- **Monitoring:** Assesses the quality of performance over time and ensures that the findings of audits and other reviews are promptly resolved.

According to the internal control standards, these five components must be effectively operating together in an integrated manner to provide assurance that operations, reporting, and compliance objectives are met. Management is responsible for an effective internal-control system. As part of this responsibility, management sets the entity's objectives, implements controls, and evaluates the internal control system.

FCC Has Designed Some TRS Internal Controls That Address Compliance and Reporting

FCC has designed some internal controls that focus on program compliance and reporting objectives. In response to TRS fraud, first identified by the FCC OIG audits of TRS providers, FCC implemented rule changes. FCC OIG officials told us that they first became suspicious of possible fraudulent activity in the TRS program based on particular reimbursement claims that they judged to be unusual. They told us that at the time there was insufficient scrutiny of call data for irregularities by NECA, the TRS Fund administrator. The FCC OIG began a formal investigation of the TRS program in 2008.³³ As a result of the joint investigation among FCC's OIG, the Department of Justice, the Federal Bureau of Investigation, and the United States Postal Service, 26 people were charged in a scheme to steal more than \$50 million from the TRS Fund.³⁴ FCC has addressed many of the vulnerabilities identified by the OIG through numerous rulemakings. For example, from 2010 through 2013, FCC, among other things, designed control activities to address specific fraud risks:

- **Prohibited per-minute reimbursement for internal calls:** To address provider practices intended to inflate call minutes, FCC reiterated its policy that calls made by or to employees of VRS providers were not eligible for compensation from the TRS Fund on a per-minute basis.³⁵
- **Eliminated subcontracting:** In 2011, FCC changed the certification eligibility requirements for TRS providers to require that all Internet-based providers be directly certified by the FCC. Prior to this order, providers who were certified by FCC or by a state commission were allowed to subcontract some of the provision of services to third parties that did not have to be certified. FCC officials and other stakeholders told us that much of the fraud that had occurred in the VRS program was related to these non-certified subcontractors, specifically in the form of inappropriately generating minutes. Now that all providers are directly certified, fraud in the VRS market has decreased dramatically, according to FCC.³⁶
- **Strengthened certification:** In 2011, FCC amended the TRS certification process to require that providers submit evidence demonstrating compliance with FCC's rules and authorizing on-site inspections of providers' facilities.³⁷ In 2013, FCC further

changed provider certification rules to require providers' senior managers to sign under penalty of perjury that their companies' claims for compensation from the fund were valid and that the data they reported were true and accurate.³⁸ This change was implemented to deter fraudulent activity and further ensure that providers' senior managers were diligent in verifying the information they submitted for reimbursement.

- **Strengthened user registration rules:** In 2012, the Commission implemented a rule that prohibited IP Relay providers from handling non-emergency calls made by first-time users without first verifying the user's registration information.³⁹ Prior to this rule change, IP relay services entailed some degree of anonymity of end users and provided the technical ability to mask one's calling location. Some individuals exploited this anonymity by using IP relay services to perpetrate scams and other types of abuse. In 2013, FCC also established new VRS registration rules to address the problems of fraud, waste, and abuse by improving the mechanism by which VRS users are verified. The new rule requires VRS users to register with each provider they use and certify that they had a qualifying disability. Users were also given a 10-digit number that was associated with their registered account. According to FCC officials, this change has drastically reduced the number of fraudulent calls placed through the TRS program.

In addition to these controls, FCC has also implemented controls with regard to the TRS Fund's administrator and routine audits of the program. FCC better defined the role of the fund administrator in the contract it entered with RLSA. Among other things, the contract outlined the fund administrator's roles in collecting, disbursing, and protecting TRS funds; in providing routine reports to FCC on the status of the fund; and in analyzing provider data for irregularities and withholding compensation when appropriate. FCC has also implemented an audit program, with audits conducted by the OIG, which includes periodic audits on the fund administrator and audits of service providers to ensure compliance with several TRS program rules. Since 2008, the OIG has conducted one audit of the fund administrator and 33 audits of providers.⁴⁰ OIG officials told us that their audits of TRS have focused on fraud and financial risks to the TRS Fund rather than risks related to the overall management of the TRS program or the quality of the relay services provided to customers.

FCC Lacks a Comprehensive Internal Control System to Manage TRS Program Risks

FCC has designed some internal controls for the TRS program, particularly with respect to program compliance; however, as previously discussed, FCC does not have clear program performance goals. Without performance goals, it is difficult to create a comprehensive internal control system which identifies and manages the risks to achieving the program's goals. It is clear from FCC's agency-wide plans and program-specific orders that combating fraud is a priority, and FCC has designed a number of controls to do so. But the purpose of the TRS program is to provide functionally equivalent telecommunications to persons with hearing or speech disabilities. Thus, it is important that FCC's internal control system be designed around identifying and addressing risks to providing functionally equivalent service,

of which fraudulent activity would be one risk. We compared FCC's control system with *Green Book* standards and found several instances where practices were not aligned. These instances, among others, create risks that program's resources are not being effectively used to achieve the program's purpose.

- **Risk Assessment:** Internal control standards call for a risk assessment that will identify risks, both internal and external, and analyze the risks for possible effects. Risk assessments are then used to help management formulate an approach for risk management. According to documents provided by FCC, the last risk assessment of the TRS program was conducted in 2013. FCC's risk assessment of the TRS program was a one-page document that did not comprehensively identify risks or considerations of all interactions between FCC and external parties. We found that the risk assessment focused on fraud, waste, and abuse and did not look at other risks to achieving the provision of functionally equivalent telecommunications to persons who are deaf, hard of hearing, or have speech disabilities. Six total risks were identified, none of which was specific to TRS. For example, one of the six risks identified in the TRS risk assessment was the "failure by management to recognize fraud in FCC programs."
- While it is important that fraud risks and risks to program resources are identified and addressed to keep the program efficient and viable, the *Green Book* and other internal control guidance state that a risk assessment should identify all relevant risks posed to achieving program goals.⁴¹ Without a robust risk assessment of the TRS program, FCC may not be able to identify and address the relevant risks to ensuring the provision of functionally equivalent telecommunications to people with hearing and speech disabilities.
- **Information and communication:** Internal control standards call for effective external communications to those groups that can have an impact on programs; such groups in the case of TRS, would include TRS users and service providers. TRS rules are contained in federal regulations,⁴² and FCC program policies are explained across numerous reports and orders. Six of 10 providers told us about challenges understanding the program's rules that applied to them in part because rules for a specific type of TRS service are discussed throughout FCC orders rather than compiled in one place for each type of TRS service. As an example, we found changes affecting IP Relay services incorporated into the 2013 VRS Reform Order. Specifically, among other things, the order modifies the rules so that all Internet-based providers are required to obtain individual user consent before a default provider change may occur. Thus, a provider of IP CTS, for example, might not know that rules for its service were part of a VRS order and could be unaware of changes affecting its company. Further, this issue was highlighted in a 2008 OIG audit of the program when the OIG recommended that FCC develop a TRS handbook for providers to supplement FCC rules and consolidate TRS program and administrative policies into a single reference guide. FCC officials told us that such a TRS handbook has not been created because they have prioritized other activities in managing the TRS program. In 2011, FCC, in observing that TRS rules had become

“somewhat unwieldy” since 2000, sought comment on whether to reorganize section 64.604 of its rules, which pertains to the TRS program.⁴³

FCC did not act on that proposal, but in 2013 proposed instead to revise the structure of its rules so that they are service specific and transmission specific, where appropriate, and sought comments more broadly on how best to reorganize its rules to improve program clarity. To date, FCC has not improved its external communications to program users or providers through better organization of TRS rules and regulations nor provided any specific time frames for doing so.

- **Monitoring.** Monitoring can include, for a program like TRS that serves the public, the analysis of consumer complaints. Such complaints may indicate that deficiencies exist—deficiencies that could be investigated to determine any possible underlying causes. FCC aggregates the TRS consumer complaints filed with FCC, state regulators, and providers, as well as aggregating complaints by service, complaint type, and the amount of time it takes to resolve them. For example, 76 percent of the 272 TRS complaints were about VRS. The types of TRS complaints most frequently received included complaints about customer service, interoperability of a consumer’s equipment with a service provider’s network, and “slamming” and “porting.”⁴⁴

Subsequent to our request for any analyses FCC may have conducted on TRS complaints, FCC began conducting an analysis in August 2014 on complaints received from July 1, 2013, through June 30, 2014.⁴⁵ According to FCC, there had not been any analysis like this conducted before. As a result of not routinely analyzing consumer complaints about TRS, FCC was missing an opportunity to monitor the TRS program and to proactively identify recurring issues, trends, and potential risks to the program and determine if corrective actions were needed.

We have previously examined and noted concerns with FCC’s complaint process and recommended that FCC expand its outreach to consumers about this process and establish policies and procedures for monitoring and analyzing trends in consumer complaints, among other things.⁴⁶ FCC agreed with our prior recommendation and, with regard to TRS, officials told us that they plan to routinely analyze TRS complaints going forward. In January 2015, FCC launched a new online consumer help center, which, according to FCC, will make it easier for consumers to file complaints and help streamline FCC’s process for synthesizing and analyzing trends in consumer complaints. Such analyses could help provide FCC with useful TRS data to help it make performance-based decisions and evaluate its efforts with regard to management of the TRS program.

STAKEHOLDERS CITED SEVERAL CHALLENGES TO TRS SERVICE QUALITY AND COMPETITION

Stakeholders Identified Challenges to Providing High Quality Services

Consumer groups and TRS providers identified, through interviews and a survey, the following challenges to TRS service’s quality: the lack of skill-based routing, interpreter accuracy, and decreasing TRS reimbursement rates.

Skill-Based Routing

Some of the consumer groups told us that the lack of skill-based routing—which would allow users making a TRS call to request a CA with a particular specialty, such as a medical or legal expertise—negatively affects TRS service quality. For example, one consumer group representative told us that under the current program a TRS user’s assignment is based on interpreter availability. The expectation that interpreters will be the best fit for all calls is not reasonable and can lead to poor communication, especially during medical or legal calls. In addition, 7 of the 10 providers responding to our survey said that the lack of skill-based routing leads to lower quality service (see app. II for our survey results). Some consumer groups have requested that VRS providers be allowed, or required, to offer skill-based routing. FCC is not in favor of compensating VRS providers for skill-based routing services due in part to a number of implementation issues. For example, FCC pointed out in its 2013 VRS Reform Order that skill-based routing implementation issues include how to reconcile a skill-based routing function with the requirement that VRS calls be answered in the order received, the availability of CAs to meet speed of answer requirements, determining the appropriate skills needed for specialized routing, and determining if skill-based routing should be mandatory or voluntary.⁴⁷

Interpreter Accuracy

Some consumer groups we interviewed identified interpreter accuracy as a TRS service quality challenge. Specifically, according to one consumer group, the wide range of skill levels across CAs creates the greatest challenge to users in obtaining accurate interpretation. They noted that some interpreters do not have the required skill level to ensure accuracy, a circumstance that can lead to misunderstandings between the two participants. FCC officials noted that TRS rules allow users to request a change in the interpreter when the user determines that effective communication is not occurring. FCC requires interpreters to be “qualified” but leaves it to the providers to make that determination.⁴⁸ FCC officials told us that some providers employ only certified interpreters to meet this requirement, while other providers use their own testing and evaluation methods to determine which interpreters are qualified.

TRS Reimbursement Rates

According to providers, decreasing the amount that TRS providers are reimbursed for their services can affect a company’s ability to hire and retain qualified interpreters. For example, 8 of 10 providers responding to our survey indicated that the current TRS reimbursement rates make it much more difficult to hire and retain qualified interpreters. Decreases in TRS reimbursement rates, according to one provider, have led some providers to find ways to cut costs by hiring less skilled—and therefore less expensive—CAs. However, there appears to be disagreement between VRS providers and FCC about whether VRS reimbursement rates are set at appropriate levels. According to the 2013 VRS Reform Order, in setting TRS Fund compensation rates for VRS for the 2010–11 fund year, FCC found that in the prior 4 years—where the rates had been set based on providers’ projected costs—providers had been overcompensated by more than \$2.00 per minute as a result of a reliance on projected costs and inaccurate demand forecasts submitted by providers.⁴⁹

Stakeholders Identified Challenges to Encouraging Competition and Technological Innovation

Consumer groups and TRS providers identified, through interviews and a survey, the following TRS-related competition challenges: TRS rate reductions,⁵⁰ the lack of compensation for marketing and outreach and research and development, and the lack of interoperability between VRS providers.

TRS Rate Reductions

The amount of compensation TRS providers receive has decreased over time, specifically, for VRS services.⁵¹ For example, as previously discussed, VRS rates have decreased from 2003 to 2015.⁵² Providers noted that the rate reductions have affected competition. Specifically, all 10 providers stated that TRS rate reductions decreased competition, with 6 of those providers stating that TRS rate reductions significantly decreased competition. Both providers and some consumer groups told us that TRS rate reductions have prevented new entrants from coming into the market and subsequently limited the number of providers a user can choose from. Further, providers told us rate reductions and increases in compliance requirements will lead more providers to exit the market. However, FCC stated in its 2013 VRS Reform Order, that there is no evidence proving that per-minute costs have dropped dramatically based on the current TRS-fund administrator's recalculated average of providers' current reported per-minute costs.⁵³ In addition, according to FCC, there are other reasons outside of rate reductions that could compel a provider to leave the market, such as a provider's inability to compete effectively with other more efficient providers.

We conducted a market concentration analysis and found that competition among TRS providers is decreasing as the number of providers for most TRS services is decreasing. For example, the number of TRS providers has decreased from rate years 2008 through 2014 for all six TRS services except IP CTS. (See app. III for more detailed results of our market concentration analysis.) In addition, the VRS and IP CTS services, which have more providers and may appear to have the most competition, are dominated by a few providers. Our analysis found that in 2013–2014 rate year the top VRS provider controlled most of the VRS market while the top three IP CTS providers controlled over 98 percent of the market, based on total minutes of service provided.⁵⁴

Lack of Compensation for Marketing and Outreach and Research and Development

Most TRS providers noted that the lack of compensation for marketing and outreach and research and development hinders competition. For example, 7 out of 10 providers stated that the lack of compensation to TRS providers for marketing and outreach has significantly decreased their ability to compete. According to one provider, a provider's marketing and outreach efforts cut significantly into a provider's profit margin, and as a result, the lack of marketing and outreach compensation discourages new entrants into the market and inhibits a provider's ability to attract new customers through marketing efforts. According to FCC officials, they no longer reimburse providers' marketing and outreach efforts because they cannot effectively determine whether there is a sufficient amount of potential new customers to warrant such an incentive. In addition, FCC stated in its 2013 VRS Reform Order that the majority of TRS's marketing compensation appear to have been used by providers to promote

individual-branded marketing campaigns focused on winning back TRS users from competitors rather than informing the general public about the nature and functions of relay services.⁵⁵

As mentioned, according to FCC officials, FCC ceased marketing compensation to providers and called for the creation of a national marketing and outreach pilot program that will, according to the 2013 VRS Reform Order, seek to ensure that potential TRS users and the general public are aware of the TRS program and its role in providing functionally equivalent services.⁵⁶ The 2013 VRS Reform Order outlined a nationwide TRS marketing and outreach pilot program that is intended to, among other things, establish clear messaging about the purposes, functions, and benefits of IP Relay and VRS; educate consumers who are deaf, hard of hearing, or have speech disabilities about broadband adoption programs available to low-income families; provide materials to local, state, and national governmental agencies on the purposes, functions, and benefits of IP Relay and VRS; and explore opportunities to collaborate with other entities to disseminate information about IP Relay and VRS. The 2013 VRS Reform Order called for the selection of either (1) “outreach coordinators” who will conduct and coordinate IP Relay and VRS outreach nationwide and will be compensated through the TRS Fund or (2) an FCC contract with the TRS Fund administrator to enter into a similar arrangement.⁵⁷ According to the 2013 VRS Reform order, the TRS outreach coordinators will not be affiliated with any TRS provider and they will disseminate non-branded information to potential new users and to the general public about IP Relay and VRS, the purposes and benefits of the services, and how to access and use the services.⁵⁸

According to most TRS providers, the elimination of compensation for research and development has also reduced competition and limited innovation. For example, 7 out of 10 providers stated that the lack of compensation from FCC to TRS providers for research and development significantly decreases their ability to compete. Specifically, one provider noted that the lack of compensation for research and development reduces a provider’s ability to compete through quality service improvements and innovations, such as new and unique provider-specific features including improved software functionality, enhancing VRS picture quality, or increasing captioning speed and accuracy during IP CTS sessions. However, according to FCC, TRS research and development compensation is inefficient and duplicative. FCC stated in its 2013 VRS Reform Order that TRS research and development reimbursement would allow for duplicative spending because multiple providers would be able to expend research and development funds on similar or identical enhancements and would not share the results with potential or existing competitors.⁵⁹ In addition, the 2013 VRS Reform Order, among other things, directed the FCC Managing Director to enter into an arrangement with the National Science Foundation to conduct research to ensure that TRS is functionally equivalent to voice telephone services and to improve the efficiency and availability of TRS.⁶⁰ According to FCC officials, in January 2015, FCC and MITRE entered into a memorandum of understanding to conduct this research. FCC officials told us that the research project establishes a Center of Expertise that is intended to bring together experts, representatives of the community of persons with hearing or speech disabilities, and other stakeholders to prioritize and address the needs of TRS users. According to FCC officials, the Center of Expertise held its inaugural meeting in March 2015.

Lack of Interoperability among VRS Providers

The majority of VRS providers stated that the lack of interoperability among VRS providers can inhibit competition. For example, 5 out of 6 VRS providers stated that the lack of interoperability can lead to significantly less competition. Multiple providers told us, while interoperability of VRS equipment is required by FCC, 61 some services are still not interoperable with other providers' equipment and, as a result, one provider told us that they filed a petition with FCC.

To address interoperability, improve competition, and quality, FCC proposed instituting and transitioning to a VRS Advanced Video Communication Platform (formerly known as Neutral Video Communication Service Platform).⁶² According to the 2013 VRS Reform Order, a neutral video communication service provider will have multiple benefits, specifically: more effective and efficient competition on the basis of service quality, including interpreter quality and the capabilities to handle the varied needs of VRS, and more efficient and effective VRS CA service competition through the elimination of new entrant barriers such as the cost of building and maintaining a video communication service platform.⁶³ In addition, the 2013 VRS Reform order directed FCC's Managing Director to select a neutral third party to build, operate, and maintain the Advanced Video Communication Platform.⁶⁴ In the order, FCC stated that it would contract out the above services and responsibilities to a third party and that party would be compensated through the TRS Fund.⁶⁵ However, FCC officials stated that this procurement has been cancelled because prices were too high and the agency determined that it would not be in the federal government's interest to accept any of the proposals submitted. Contrary to FCC's perspective about the benefits of the Advanced Video Communication Platform, a majority of the providers responding to our survey stated that the platform will not improve competition. Specifically, 6 of 10 providers stated that the Advanced Video Communication Platform will reduce competition. One provider told us that the Advanced Video Communication Platform could disincentivize new companies from entering the market because existing TRS requirements, such as 24-hour staffing of interpreters, could still be in effect under the proposed Advanced Video Communication Platform. Therefore, according to the provider, labor costs could prevent new entrants from making profits.

Some consumer groups and providers told us that the Advanced Video Communication Platform could stifle innovation. For example, the Advanced Video Communication Platform request for proposal included a number of core features that all participating providers will use and offer to its customers. As a result, according to one provider, VRS providers would have to give up their proprietary technology and ultimately become a provider of interpretation services, rather than competing on unique and provider specific technological features in addition to interpretation. For example, another provider told us that as a result of a transition to an Advanced Video Communication Platform, existing innovative provider-specific features would no longer be available and subsequently replaced by Advanced Video Platform features. Since Advanced Video Platform features will be the same for all providers—as are reimbursement rates—competition will shift from which company has the best features to which company has the best interpreters. FCC is in the beginning stages of developing the Advanced Video Communication Platform, so it is unclear at this point how it will affect VRS service quality and competition.

CONCLUSION

Since 2002, annual TRS Fund expenditures have grown by over \$700 million. A variety of factors contributed to this growth, including the development of Internet-based TRS services, increased TRS usage, and some fraud in VRS and IP Relay. The size of the TRS Fund is likely to continue to rise as more persons with hearing or speech disabilities learn about these services and the hard-of-hearing population increases as the baby boomers age. FCC's fraud reduction efforts contributed to the decreases in total TRS costs that occurred in 2010 and 2011. FCC must continue to be vigilant about fraud, especially as new technologies emerge that could require the development of new internal controls. Beyond fraud reduction efforts, however, it is important that the TRS program be managed in a proactive manner that is in accordance with leading management practices. If, for example, FCC does not develop specific multiyear and intermediate goals that are objective, quantifiable, and measurable and that have performance indicators, targets, and time frames, it becomes difficult to determine whether FCC has met the program's purpose of providing functionally equivalent services. Developing linked, TRS-specific performance goals and measures; conducting a full TRS program risk assessment; and consolidating rules and procedures for each TRS service will help ensure that FCC is managing the program in a proactive, result-oriented manner and, ultimately, that the TRS program is meeting its overall purpose of providing functionally equivalent telecommunications services to persons who are deaf, hard of hearing, or have speech disabilities.

RECOMMENDATIONS FOR EXECUTIVE ACTION

To improve performance management of the Telecommunications Relay Service, we recommend that the Chairman of the Federal Communications Commission take the following three actions.

- Develop specific performance goals and measures for the TRS program. FCC should establish goals that would guide its efforts on major program dimensions—for example, consider goals and performance measures related to, but not limited to, service quality or competition among providers.
- Following the establishment of TRS's performance goals, conduct a robust risk assessment that can help FCC design a comprehensive internal-control system.
- Improve FCC's communication of TRS rules and procedures to the community of individuals who are deaf, hard of hearing, or have speech disabilities and the companies providing TRS services through the creation and dissemination of a handbook, program manual, or other consolidation of TRS rules and procedures.

AGENCY AND THIRD-PARTY COMMENTS

We provided a draft of this report to FCC and RLSA for their review and comment. FCC agreed with our recommendations and discussed actions it plans to take to implement the

recommendations. FCC also e-mailed technical comments, which we incorporated as appropriate. RLSA did not have comments on the report.

Sincerely yours,
Mark L. Goldstein
Director, Physical Infrastructure Issues

APPENDIX I: OBJECTIVES, SCOPE, AND METHODOLOGY

The objectives of this report were to examine (1) how the services and costs of the Telecommunications Relay Service (TRS) program have changed since 2002; (2) the Federal Communication Commission's (FCC) performance goals and measures for the TRS program and how they compare with key characteristics of successful performance goals and measures; (3) the extent to which the design of the TRS program's internal control system identifies and considers program risks; and (4) the challenges, if any, that exist in ensuring quality services for users and a competitive environment for providers. The scope of our audit did not include the testing of specific internal control activities.

To determine how the costs and services of the TRS program have changed since 2002, we reviewed FCC documents, including FCC orders and stakeholder comments in FCC rulemaking proceedings. In addition, we reviewed FCC's OIG, GAO, Congressional Research Service, and consumer group reports on TRS. We also collected and analyzed TRS program data on costs and minutes of usage for all six major forms of TRS from 2002–2014. We assessed the reliability of these data through conversations with FCC and RLSA officials about how the data are gathered and maintained. We determined the data were sufficiently reliable for the purposes of showing trends in program usage and costs. We selected 2002 for the scope of our review as that was the year when Video Relay Service (VRS)—a popular form of TRS—was first made widely available. We interviewed:

Agencies

Federal Communications Commission
Federal Communications Commission-Office of Inspector General

TRS Fund Administrators

National Exchange Carrier Association Rolka Loube Saltzer Associates

Associations

American Association of the Deaf-Blind
Association of Late Deafened Adults
Cerebral Palsy and Deaf Organization
Hearing Loss Association of America
National Association of the Deaf
Telecommunications for the Deaf, Inc.
Registry of Interpreters for the Deaf

TRS Providers

American Sign Language Services, Inc.

AT&T Inc.

Communication Access Ability Group

Convo Communications

CSDVRS

Hamilton Relay

InnoCaption, Inc.

Purple Communications, Inc.

Sorenson Communications

Sprint Corporation

We analyzed these interviews to identify how and why TRS services had changed in costs and minutes from 2002-2014.

To identify FCC's performance goals and measures for the TRS program, we reviewed FCC documents, such as strategic plans and performance budgets; reviewed FCC web pages pertaining to the TRS program; and interviewed FCC officials about program goals and measures. To assess program goals and measures, we compared FCC's performance goals and measures to key characteristics of successful performance goals and measures that GAO developed in prior work, as well as to requirements contained in the Government Performance and Results Act of 1993, as amended by the GPRA Modernization Act of 2010.¹

To understand the extent to which the design of the TRS program's internal control system appropriately identifies and considers program risks, we reviewed FCC documents and rules, and spoke with FCC officials about TRS internal controls. Specifically, FCC, FCC OIG, and the current TRS Fund administrator provided us program-related documentation on risk assessments, control activities, and audits. We identified what controls were in place and then compared the design of the internal control system with the requirements contained in the GAO *Standards for Internal Control in the Federal Government (the Green Book)*.

To assess the challenges to ensuring quality services for users and a competitive environment for providers, we first identified challenges that were identified through our interviews with representatives from all 10 TRS providers, associations representing the community of persons who are deaf or hard of hearing, FCC, FCC OIG, and the current and previous TRS Fund administrators. We also reviewed TRS-related FCC orders, standards set in the Americans with Disabilities Act, and industry literature. In addition, to develop quantifiable information about the providers' views on the challenges to ensuring quality services for users and a competitive environment for providers, we developed a survey instrument for the providers. We pretested the survey with one provider to ensure that questions were clear, unbiased, comprehensive, and that terminology was used correctly. We made changes to the content of the questions in response to the pretest. We surveyed all 10 providers and received a 100-percent response rate. Because we administered the survey to the complete universe of potential respondents, there are no sampling errors. However, the practical difficulties of conducting any survey may introduce errors, commonly referred to as non-sampling errors. For example, difficulties in how a particular question is interpreted, in

the sources of information that are available to respondents, or in how the data is entered into a database or analyzed can introduce unwanted variability into the survey results. In addition, to further analyze issues related to TRS competition and market concentration, we calculated certain measures of market concentration in the two largest forms of TRS—IP CTS and VRS—and analyzed the data on TRS minutes of service from each provider from 2008–2014. We selected 2008 as the starting year for this analysis because, according to FCC officials, this was the first year with complete market concentration data on all six forms of TRS.

We conducted this performance audit from April 2014 through April 2015 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusion based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

APPENDIX II: SURVEY OF TELECOMMUNICATIONS RELAY SERVICE PROVIDERS

The questions we asked in our survey of TRS providers are shown below. Our survey was comprised of closed- and open-ended questions. In this appendix, we include all the survey questions and aggregate results of responses to the closed-ended questions; we do not provide information on responses provided to the open-ended questions. For a more detailed discussion of our survey methodology see appendix I.

Contact Information:

Please provide the name and contact information of the person completing this survey in case GAO needs to follow up on the information provided.

Name: Title:

Company:

Email: Phone:

Service Quality Questions:

1. How, if at all, have the current TRS compensation rates affected your company's ability to hire and retain qualified interpreters?

Response

Much more difficult to hire and retain	Slightly more difficult to hire and retain	No effect	Slightly easier to hire and retain	Much easier to hire and retain	Don't Know	Total Responses
8	0	2	0	0	0	10

2. Industry wide, how, if at all, has a lack of skill-based routing affected TRS consumers receiving quality service?

Response

Much higher quality service	Slightly higher quality service	No effect	Slightly lower quality service	Much lower quality service	Don't Know	Total Responses
0	0	2	2	5	1	10

3. Industry wide, how, if at all, has interpreter workload affected TRS quality?

Response

Much higher quality	Slightly higher quality	No effect	Slightly lower quality	Much lower quality	Don't Know	Total Responses
0	0	2	4	3	1	10

4. Overall, how effective is the FCC's current oversight and testing of TRS quality?

Response

Extremely effective	Very effective	Somewhat effective	Slightly effective	Not at all effective	Don't Know	Total Responses
0	0	4	6	0	0	10

5. Do you have any recommendations for how the FCC could better oversee and test TRS service quality? If so, please briefly describe below.

6. How much, if at all, will the FCC's proposed Advanced Video Communication Platform (formerly known as Neutral Video Communication Service Platform) improve service quality?

Response

A lot	A little	Not at all	Don't know	Total Responses
0	1	5	4	10

7. Please rank the following TRS quality challenges from the most significant challenge to the least significant challenge. Please place a 1 in front of the most significant challenge, 2 in front of the second, etc.

Response

Question	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
A. TRS compensation rates affect a company's ability to hire and retain qualified interpreters.	4	6	0	0	0
B. Lack of skill-based routing	0	1	5	3	1
C. Interpreter workload	0	1	4	3	2
D. FCC oversight and testing of service quality	0	2	3	1	4
E. Other [Open-ended]	6	0	0	0	0

Competition Questions:

8. How much, if at all, have TRS rate reductions affected competition in the TRS market?

Response

Significantly increased competition	Increased competition	Neither increased or decreased competition	decreased competition	Significantly decreased competition	Don't Know	Total Responses
0	0	0	4	6	0	10

9. For those services that your company provides or has provided, how much, if at all, do current TRS rates attract new companies to enter the TRS market and provide services? (Please respond "Don't provide" if your company doesn't currently or hasn't previously provided the service).

	Response					
TRS Service Type	A lot	A little	Not at all	Don't know	Don't Provide	Total
VRS	8	0	0	0	2	10
Text-to-Voice TTY-based TRS	0	1	2	0	7	10
Speech-to-Speech (STS) Relay Service	0	1	3	0	6	10
Captioned Telephone Service	0	1	2	0	7	10
Internet Protocol (IP) Relay Service	0	1	3	0	6	10
IP Captioned Telephone Service	0	2	3	0	5	10

10. How, if at all, has a lack of interoperability among providers affected competition?

Response

Significantly less competition	Moderately less competition	Slightly less competition	No effect	There is no lack of interoperability among providers	Don't Know	Total Responses
5	2	0	3	0	0	10

11. How, if at all, has the lack of compensation from the FCC to TRS providers for research and development affected your company's ability to compete?

Response

Significantly less ability to compete	Moderately less ability to compete	Slightly less ability to compete	No effect	Don't Know	Total Responses
7	1	1	1	0	10

12. How, if at all, has the lack of compensation from the FCC to TRS providers for marketing and outreach affected your company's ability to compete?

Response

Significantly less ability to compete	Moderately less ability to compete	Slightly less ability to compete	No effect	Don't Know	Total Responses
7	1	1	0	1	10

13. How, if at all, will the FCC's proposed Advanced Video Communication Platform (formerly known as Neutral Video Communication Service Platform) affect competition?

Significantly increase competition	Increase competition	Neither increase nor decrease competition	Decrease competition	Significantly decrease competition	Don't know	Total Responses
1	1	0	1	5	2	10

14. Please rank the following challenges to TRS competition from the most significant challenge to the least significant challenge. Please place a 1 in front of the most significant challenge, 2 in front of the second, etc.

Response

Question	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Total
A. TRS rate reductions	8	1	1	0	0	0	10
B. Current TRS rate's ability to attract new TRS providers	1	0	3	1	3	2	10
C. Lack of interoperability among providers	1	2	0	2	4	1	10
D. Lack of compensation for research and development	0	2	4	3	1	0	10
E. Lack of compensation for marketing and outreach	0	2	2	4	1	0	10
F. Other [Open-ended]	1	3	0	0	0	0	4

APPENDIX III: GAO ANALYSIS OF PROVIDER CONCENTRATION IN TRS PRODUCT MARKETS, 2008–2014 RATE YEARS

**Table 1. Provider Concentration in TRS Product Markets
(annually as of July 1)**

			A. Number of Providers				
TRS Products	2008	2009	2010	2011	2012	2013	2014
TTY	7	7	6	5	3	4	3
STS	7	7	6	5	3	4	NA
CTS	4	4	4	4	3	4	3
IP Relay	6	6	7	6	3	3	NA
IP CTS	NA	3	3	5	3	3	4
VRS	10	9	8	9	6	6	6
	B. Concentration Ratio of Providers by Rate Year						
TRS Products	2011–12		2012–13		2013–14		
IP CTS: Top 2 Providers	66.6%		75.2%		71.7%		
IP CTS: Top 3 Providers	99.5%		99.3%		98.6%		
VRS: Top 2 Providers	92.9%		91.2%		90.2%		
VRS: Top 3 Providers	100%		99.0%		98.7%		
	C. Herfindahl-Hirschman Index (HHI) by Rate Year						
TRS Products	2011–12		2012–13		2013–14		
IP CTS	3509		3554		3403		
VRS	6973		6791		6603		

Source: GAO Analysis of FCC data. | GAO-15-409

Notes: Under section A, number of providers was calculated in July of each year, which is beginning of the rate year

The concentration ratios and the HHI are computed for providers with complete data for the rate year; the data are not reported for other forms of TRS due to data limitations or confidentiality.

End Notes

¹ TRS is not intended for communication between two people who are deaf, hard of hearing, or speech disabled if both parties to the call are using the same type of relay service. There are circumstances in which calls between two deaf people using two different forms of TRS can be compensated. The different forms of TRS are explained later in this report.

² Pub. L. No. 101-336, § 401(a), 104 Stat. 327, 366 (1990), codified as amended at 47 U.S.C. § 225.

³ The provision of TRS services is paid for by the TRS Fund. The TRS Fund is a revolving fund financed through contributions made by all providers of interstate telecommunications services. Service provider contributions are based on a “contribution factor” that is set on an annual basis by FCC. 47 C.F.R. § 64.604(c)(5)(iii). These mandatory contributions are generally passed on to consumers as part of the cost of their telephone service.

⁴ 47 U.S.C. § 225(b)(1). States provide and pay for *intrastate* TRS services. States usually recover intrastate TRS costs through a surcharge applied to the telephone bills of all telephone customers within a state.

⁵ The TRS rate year runs from July 1 to June 30 of the following year.

⁶ VRS is an Internet-based form of TRS that allows persons whose primary language is American Sign Language (ASL) to communicate with a CA in ASL using video conferencing equipment.

⁷ At the time of the request, Senator Sessions was the Ranking Member of the Senate Committee on the Budget.

⁸ GAO developed a set of key practices based on analyses of leading results-oriented organizations, management studies of 23 large federal departments and agencies, and a body of literature on management reform, strategic planning, and performance measurement. See GAO, *Executive Guide: Effectively Implementing the Government Performance and Results Act*, GAO/GGD-96-118 (Washington, D.C.: June 1996).

⁹ Pub. L. No. 111-352, 124 Stat. 3866 (2011).

- ¹⁰ GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00.21.3.1 (Washington, D.C.: November 1999). The scope of our audit did not include the testing of specific internal control activities.
- ¹¹ We selected 2008 as the starting year for this analysis because, according to FCC officials, this was the first year with complete market concentration data on all 6 forms of TRS.
- ¹² 47 U.S.C. § 225. Although TRS can be considered a universal service program in that it seeks to make telecommunications services accessible to all citizens, specifically those with hearing or speech disabilities, the program is distinct from FCC's four universal service programs under the Universal Service Fund. 47 U.S.C. § 254. Those programs are the High Cost program, which seeks to bring affordable telecommunications services to those in rural areas; the Low Income program, which seeks to bring affordable telecommunications services to low income individuals; the E-rate program, which funds telecommunications services to eligible schools and libraries; and the Rural Health Care Fund, which funds telecommunications services for rural health care providers. The construct of the four universal service programs are similar to TRS in that they are managed by FCC, but the daily administration of the Universal Service Fund is handled by the Universal Service Administrative Company. For more information on the Universal Service Fund and universal service programs, including a list of related GAO reports, see GAO, *Opportunities to Reduce Potential Duplication in Government Programs, Save Tax Dollars, and Enhance Revenue*, GAO-11-318SP (Washington D.C.: Mar. 1, 2011), 194–197.
- ¹³ According to the National Association of the Deaf, users generally pay for equipment, such as telephones and computers, and service, such as Internet and telephone, although some providers have given away telephones to encourage the deaf and hard of hearing to use their TRS service.
- ¹⁴ FCC stated that some of these VRS numbers are assigned to devices with multiple users (e.g., a household with more than one deaf individual) and some users have more than one number (e.g., one number at home and another at work).
- ¹⁵ Providers submit monthly reports of minutes to the fund administrator for compensation from the fund. The reports are then to be reviewed by the fund administrator to ensure that the minutes were handled in compliance with the Commission's rules and orders before reimbursements are made. 47 C.F.R. § 64.604(c)(7)(E).
- ¹⁶ We did not evaluate the methodologies behind how FCC established reimbursement rates for each TRS service.
- ¹⁷ See *In the Matter of Structure and Practices of the Video Relay Service Program*, Report and Order and Further Notice of Proposed Rulemaking, 28 FCC Rcd. 8618 (2013) *vacated in part*, 765 F. 3d 37 (D.C. Cir. 2014). (VRS Reform Order).
- ¹⁸ The investigations resulted in four actions, the assessment of penalties, and repayments to the TRS Fund. See, e.g., *Purple Communications, Inc, Notice of Apparent Liability for Forfeiture*, 29 FCC Rcd. 5491 (2014).
- ¹⁹ According to FCC officials, the Nigerian scam calls that took place through IP Relay involved the fraudulent use of stolen credit cards to order large quantities of goods from American merchants via the anonymity of IP Relay.
- ²⁰ *In the Matter of Structure and Practices of the Video Relay Service Program*, 28 FCC Rcd. 8618 (2013) (Report and Order and Further Notice of Proposed Rulemaking).
- ²¹ GAO, *Executive Guide: Effectively Implementing the Government Performance and Results Act*. GAO/GGD-96-118. (Washington, D.C.: June 1996).
- ²² 47 U.S.C. § 225.
- ²³ Pub. L. No. 103-62, § 4, 107 Stat. 286 (1993), codified at 31 U.S.C. § 1105(a).
- ²⁴ GAO, *Agency Performance Plans: Examples of Practices That Can Improve Usefulness to Decisionmakers*. GAO/GGD-99-69 (Washington, D.C.: February 1999).
- ²⁵ VRS Reform Order.
- ²⁶ 47 C.F.R. § 64.604.
- ²⁷ According to FCC officials, FCC exercises its enforcement authority to review and audit the accuracy of provider certifications, and takes enforcement action against providers that do not comply with FCC minimum standards.
- ²⁸ According to the Government Performance and Results Act, “outcome measures” are assessments of the results of a program compared to its intended purpose, and “output measures” are the tabulations, calculations, or recordings of activities or efforts and can be expressed in a quantitative or qualitative manner.
- ²⁹ GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00.21.3.1 (Washington, D.C.: November 1999).
- ³⁰ 31 U.S.C § 3512.
- ³¹ GAO, *Internal Control Management and Evaluation Tool*, GAO-01-1008G (Washington, D.C.: August 2001).
- ³² OMB, *Management's Responsibility for Internal Control*, Circular A-123 (Washington, D.C.: December 2004).
- ³³ The Enforcement Bureau also began analyzing provider call records during this period and identified practices that resulted in inflated call minutes.

- ³⁴ FCC, *FCC Chief of Staff Praises Decisive Action to Prosecute Fraud in VRS Program*, Press Release (Washington, D.C.: Nov. 19, 2009).
- ³⁵ *In the Matter of Structure and Practices of the Video Relay Service Program*, Declaratory Ruling, 25 FCC Rcd. 1868, 1869-70, 3-5 (2010).
- ³⁶ The scope of our review did not include testing for fraudulent activity. The FCC OIG continues to conduct audits of TRS providers aimed at uncovering fraud, waste, and abuse in the TRS program. In March 2014, it was announced that investigations by the FCC OIG, the Department of Justice, and the Federal Bureau of Investigation, had led to VRS fraud indictments against two people, bringing the total number of people and business entities indicted for VRS fraud to 31.
- ³⁷ *In the Matter of Structure and Practices of the Video Relay Service Program*, Second Report and Order, 26 FCC Rcd. 10898 (2011).
- ³⁸ *In the Matter of Structure and Practices of the Video Relay Service Program*, Report and Order and Further Notice of Proposed Rulemaking, 28 FCC Rcd. 8618 (2013).
- ³⁹ *In the Matter of Misuse of Internet Protocol (IP) Relay Service; Telecommunications Relay Services for Individuals with Hearing and Speech Disabilities*, First Report and Order, 27 FCC Rcd 7866, 13 n.53 (2012).
- ⁴⁰ According to the OIG, 28 of these audits are complete and five are in process.
- ⁴¹ According to internal control standards, a precondition to risk assessment is the establishment of clear, consistent agency goals and objectives. As discussed, FCC has not yet established clear performance goals for the TRS program.
- ⁴² 47 C.F.R. Part 64, Subpart F.
- ⁴³ 47 C.F.R. § 64.604.
- ⁴⁴ In general, “slamming” occurs when a VRS provider changes a consumer’s preferred VRS provider without the customer’s permission. “Porting” involves changing the preferred VRS provider at the request of the consumer. Porting problems may arise if the exiting service provider is not cooperative in releasing the consumer’s telephone number to the consumer’s new relay service provider.
- ⁴⁵ FCC’s analysis is available at https://apps.fcc.gov/edocs_public/attachmatch/DOC331113A1.docx.
- ⁴⁶ See GAO, *Telecommunications: FCC Needs to Improve Oversight of Wireless Phone Service*, GAO-10-34 (Washington, D.C.: Nov. 10, 2009).
- ⁴⁷ VRS Reform Order, 180.
- ⁴⁸ According to FCC officials, the standard for interpreters to be qualified is that they must be able to interpret expressively and receptively, using specialized vocabulary. FCC officials said that the standard is based on case law derived from the ADA.
- ⁴⁹ VRS Reform Order, 183.
- ⁵⁰ TRS rate reductions refer to reductions in the reimbursement rates of VRS and IP Relay.
- ⁵¹ VRS services make up about 70 percent of the payments to providers of all TRS providers from the TRS Fund, which makes VRS the largest TRS market in terms of compensation.
- ⁵² VRS rates went from \$17 per minute for all VRS providers in 2003 to \$5.29 per minute for tier I VRS providers, \$4.82 per minute for tier II VRS providers, and \$4.25 per minute for tier III VRS providers in 2015.
- ⁵³ VRS Reform Order, 191.
- ⁵⁴ Our market concentration analysis measured the extent to which the activities in the TRS market are controlled by a few providers. We measured TRS provider concentration by calculating the number of providers, the concentration ratios of the top providers, and the Herfindahl-Hirschman Index (HHI), which account for the size-distribution of providers or the relative influence of both small and large providers in the market.
- ⁵⁵ *In the Matter of Structure and Practices of the Video Relay Service Program*, Report and Order and Further Notice of Proposed Rulemaking, 28 FCC Rcd. 8618, 31 (2013) (VRS Reform Order).
- ⁵⁶ VRS Reform Order, 33.
- ⁵⁷ VRS Reform Order, 33.
- ⁵⁸ VRS Reform Order, 34.
- ⁵⁹ VRS Reform Order, 21.
- ⁶⁰ VRS Reform Order, 22.
- ⁶¹ *In the Matter of Telecommunications Relay Services and Speech-to-Speech Services for Individuals with Hearing and Speech Disabilities*, Declaratory Ruling and Further Notice of Proposed Rulemaking, 21 FCC Rcd. 5442 (2006).
- ⁶² According to FCC’s 2013 VRS Reform Order, an Advanced Video Communication Platform allows a registered Internet-based VRS user to use VRS access technology to make and receive VRS and point-to-point calls through a VRS CA service provider. The functions provided by the Advanced Video Communication Service Platform include the provision of a video link, user registration and validation, authentication, authorization,

ACD platform functions, routing (including emergency call routing), call setup, mapping, call features (such as call forwarding and video mail), and such other features and functions not provided by the VRS CA service provider. VRS Reform Order 89.

⁶³ VRS Reform Order 90.

⁶⁴ VRS Reform Order 93.

⁶⁵ VRS Reform Order 93.

End Note for Appendix I

⁶⁶ Pub. L. No. 103-62, 107 Stat. 285 (1993), as amended by Pub. L. No. 111-352, 124 Stat. 3866 (2010).

Chapter 38

VIDEO RELAY SERVICE: PROGRAM FUNDING AND REFORM*

Patricia Moloney Figliola

SUMMARY

The Federal Communications Commission (FCC) regulates a number of disability-related telecommunications services, including video relay service (VRS). VRS allows persons with hearing disabilities, using American Sign Language (ASL), to communicate with voice telephone users through video equipment rather than through typed text. VRS has quickly become a very popular service, as it offers several features not available with the text-based telecommunications relay service (TRS).

The FCC has adopted various rules to improve VRS service. Now VRS providers must answer 80 percent of all VRS calls within 120 seconds. VRS providers must also offer the service 24 hours a day, seven days a week. Additionally, in June 2010, the FCC began a comprehensive review of the rates, structure, and practices of the VRS program to minimize waste, fraud, and abuse and update compensation rates that had become inflated above actual cost. Rules in that proceeding were issued in June 2013. The new rules initiated fundamental restructuring of the program to support innovation and competition, drive down ratepayer and provider costs, eliminate incentives for waste, and further protect consumers. In addition, the new rules transition VRS compensation rates toward actual costs over the next four years, initiating a step-by-step transition from existing tiered TRS Fund compensation rates toward a unitary, market-based compensation rate.

Congressional interest in the VRS program is twofold: eliminating fraud and abuse in the program and maintaining the usefulness of the program for users. Controversy has arisen over the latest proposals for change to the program being considered by the FCC. The FCC believes that rate structure changes are needed to reduce fraud and better manage the VRS program, but the deaf and hard-of-hearing community is concerned that funding cuts will result in fewer and less-qualified ASL interpreters. Additionally, the FCC has proposed changing the technologies used to operate and use the system, but the

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community is concerned that changes in technology will decrease the quality of the system as it is now and also potentially pose challenges to some users.

INTRODUCTION: HOW VIDEO RELAY SERVICE WORKS

The Federal Communications Commission (FCC) regulates a number of disability-related telecommunications services, including video relay service (VRS). VRS is a form of telecommunications relay service (TRS).¹ The service allows persons with hearing disabilities, using American Sign Language (ASL), to communicate with voice telephone users through video equipment rather than through typed text. Video equipment links the VRS user with a “communications assistant” (CA) so that the VRS user and the CA can see and communicate with each other in signed conversation (see *Figure 1*).

VRS has quickly become a very popular service. It offers several features not available with the text-based TRS:

- People with hearing disabilities can communicate using ASL rather than typing what they want to say. This allows them to incorporate facial expressions and body language into their conversations, which cannot be done using text.
- A VRS call is more like a telephone conversation between two hearing persons. For example, the parties can interrupt each other. The parties cannot interrupt each other during a traditional TRS call because the parties have to take turns communicating with the CA.
- Conversation flows more naturally between the parties, so the conversation may take place more quickly than with TRS.
- VRS calls may be made between ASL users and hearing persons speaking either English or Spanish.



Source: Gallaudet University, “Accessible Emergency Notification and Communication: State of the Science Conference (Presentation),” http://tap.gallaudet.edu/Emergency/Nov05Conference/Presentations/maddix_files/textmostly/slide2.html.

Figure 1. How Video Relay Service Works.

VRS is different from other forms of TRS in two important ways: (1) the conversation between the VRS user and the CA is made through a video link and sign language rather than typed text; and (2) the service relies on the Internet, rather than the public telephone system, for the connection between the VRS user and the CA. Also, unlike some other forms of TRS, VRS is not mandatory.

PROGRAM OVERVIEW

VRS is free to the caller, and VRS providers are reimbursed for their costs from the TRS Fund.

Management

Since July 1, 2011, the TRS Fund has been administered by Rolka Loube Saltzer Associates, LLC (RLSA). Prior to that date, the fund was administered by the National Exchange Carriers Association.

VRS Provider Service Standards

VRS providers are subject to certain requirements and prohibitions:

- Eighty percent of all VRS calls must be answered within 120 seconds.
- Service must be offered 24 hours a day, seven days a week.
- VRS providers must provide their users with a 10-digit telephone number, so users will be able to make 911 calls and have their location data routed to the appropriate emergency agency.
- Preferential treatment of calls is prohibited. VRS (and TRS) providers must handle calls in the order in which they are received. They cannot selectively answer calls from certain consumers or certain locations.
- Equipment distributed by a certified VRS provider must be interoperable with the technology of other certified VRS providers.
- VRS (and TRS) providers may not offer financial incentives to use their service or to make more or longer VRS (or TRS) calls.

Funding

The VRS program is funded through the larger TRS Fund. The TRS Fund² is a revolving fund that is financed through contributions by all providers of interstate telecommunications services.³

Contributions are based on a “contribution factor” that is set on an annual basis by the FCC. Although the FCC generally sets a new rate each year, it maintained the 2011

contribution factor while it conducts a comprehensive review of the program begun in 2010. The current carrier contribution factor is 0.01058⁴ of a service provider's interstate telecommunications revenues during the previous calendar year.

Provider Compensation/Reimbursement

VRS compensation rates for the fund year July 1, 2015, through June 30, 2016, were established as part of a "glide path" toward cost-based levels pending the implementation of structural reforms adopted in 2015. The per-minute VRS compensation rates for the period from July 1, 2015, through December 31, 2015, are:

- Tier I (a provider's first 500,000 monthly minutes), \$5.06;
- Tier II (a provider's second 500,000 monthly minutes), \$4.82; and
- Tier III (a provider's monthly minutes in excess of 1 million), \$4.06.

The applicable per-minute VRS compensation rates for the period from January 1, 2016, through June 30, 2016, are:

- Tier I, \$4.82;
- Tier II, \$4.82; and
- Tier III, \$3.87.⁵

Based on these compensation rates, projected demand for the services, and projected fund administration expenses, the FCC adopted a funding requirement of \$1,048,050,673, and a carrier contribution factor of 0.01635.⁶

JUNE 2013 REPORT AND ORDER AND FURTHER NOTICE OF PROPOSED RULEMAKING

The FCC initiated fundamental restructuring of the VRS program to support innovation and competition, drive down ratepayer and provider costs, eliminate incentives for waste blamed for burdening the TRS Fund in the past, and further protect consumers. Measures to improve the structure and efficiencies of the VRS program while promoting consumer protection include:

- Ensuring that VRS users can easily select their providers of choice by promoting the development of voluntary, consensus interoperability and portability standards;
- Enabling consumers to use off-the-shelf tablets and smartphones for any provider's VRS services by developing and deploying a VRS application to work with these devices, based on the consensus standards;
- Creating a centralized TRS user registration database to combat fraud, waste, and abuse by ensuring VRS user eligibility;

- Encouraging competition and innovation in VRS call handling services—such as ASL interpretation—by contracting with a neutral third party to build, operate, and maintain a platform for communications services; and
- Spurring research and development on VRS services by entering into a memorandum of understanding with the National Science Foundation.

In addition, the new rules transition VRS compensation rates toward actual costs over the next four years, initiating a step-by-step transition from existing tiered TRS Fund compensation rates toward a unitary, market-based compensation rate. In this manner, VRS rates will better approximate the actual, reasonable costs of providing VRS and will considerably reduce the costs of operating the program.⁷

Further Notice of Proposed Rulemaking

In a Further Notice of Proposed Rulemaking, the FCC has proposed transitioning to a new ratemaking approach that makes use of competitively established pricing—contract prices set through a competitive bidding process—where feasible.⁸ No additional action has been taken in this proceeding.

POLICY CONSIDERATIONS

The FCC has implemented changes to the VRS program to reduce fraud and abuse, better manage the amount of money that is collected to fund the program, and take advantage of technological advancements.

The primary concern of the deaf and hard-of-hearing community appears to be that cuts to the fund may result in fewer and less-qualified ASL interpreters, which would decrease the functional equivalency of the service. Additionally, it is concerned that changes in technology—even “better” technology—will decrease competition among service providers, possibly decreasing innovation. Moreover, the community believes that changes in the technology could pose challenges to some users and make placing and receiving calls more difficult.

Congressional Considerations

The deaf and hard-of-hearing community will likely continue to contact Congress whenever changes are proposed for the VRS program. The community relies heavily on the program, so it is understandable that they might view any proposed changes with concern. However, the FCC also has a responsibility to make sure that the fund remains solvent and to take advantage of advances in technology that it has determined will improve the system. Congress may wish to monitor the current proposed changes to the system to ensure that the FCC, while working to modernize TRS technology and minimize financial abuse, also gives full consideration to the concerns of the deaf and hard-of-hearing community.

APPENDIX. HISTORY OF PROPOSED CHANGES TO THE VRS PROGRAM, 2010-2013

In June 2010, the FCC began a comprehensive review of the rates, structure, and practices of the VRS program. The goal of the review has been to reform the VRS program, which for many years had been burdened by waste, fraud, abuse, and compensation rates that had become inflated above actual cost.⁹ Thus far, the commission has acted to improve the program by:

- cutting the reimbursement rate for the bulk of VRS traffic by more than \$1.00 per minute, the first substantial VRS rate reduction in six years (June 2010);
- requiring providers to submit detailed call records to justify their requests for reimbursement (April 2011);
- instituting annual as well as unscheduled audits and banning providers from tying their employees' wages to the number of calls processed (April 2011);
- prohibiting revenue-sharing arrangements between fund-eligible service providers and unregulated companies (April 2011); and
- tightening the eligibility and certification requirements for VRS providers to ensure that only providers operating in compliance with the FCC's rules would be permitted to provide service to the public (July 2011).

The FCC estimates that its actions over the past two years have saved the program approximately \$300 million.¹⁰

October 2012 FCC Request for Additional Comment

In October 2012, the FCC asked for input on how it might change the structure of the VRS program and update the VRS contribution factor and reimbursement rate.¹¹ Specifically, the FCC asked for input on three proposals by CSDVRS, a VRS service provider: (1) potential changes to VRS access technology, (2) enhancing iTRS database operations, and (3) two rate proposals.

Proposed Changes to VRS Access Technology

In a July 2012 letter to the FCC,¹² CSDVRS proposed that the FCC facilitate the migration of all VRS access technologies from the current hardware-based and VRS-proprietary system to a

software-based and off-the-shelf application that could be used on a variety of user-selected hardware. In its request for additional comment, the FCC posed a number of questions, including, for example:

- Should the commission mandate use of a single application or allow development of multiple, interoperable applications?
- Should providers be able to continue to offer their own internally developed applications? If so, under what conditions?

- What off-the-shelf hardware and operating system platforms should be supported? Should VRS users or providers be responsible for procuring the off-the-shelf equipment used with the new application?
- How should VRS users be involved in the development, selection, certification, and ongoing enhancement of the application?
- How would users obtain support for issues relating to the application or its use on their equipment (e.g., network firewall issues, troubleshooting problems)?

Proposed Enhancements to the iTRS Database

In a separate letter to the FCC submitted in May 2012,¹³ CSDVRS proposed an industry structure in which all service providers would use an enhanced version of the TRS numbering directory to provide features such as user registration and validation, call routing, and usage accounting. This new structure would separate the video communication service component of VRS from the ASL relay CA service component by providing the functions of the video component from an enhanced database (“enhanced iTRS database”). In its request for additional comment, the FCC posed a number of questions, including, for example:

- What functions and services should the enhanced iTRS database provide?
- How would ASL relay CA service providers interface with the enhanced iTRS database?

Proposed Rate Changes

In April 2012, the FCC stated that the current interim (2011) rates for VRS would remain in place pending the completion of its VRS program review.¹⁴ The FCC has stated that it anticipates completing the proceeding prior to setting rates for the 2013-2014 fund year. It requested the fund administrator, RLSA, to submit proposed VRS rates for the remainder of the 2012-2013 fund year. In the October 2012 request, the FCC asked for comment on two proposed VRS compensation rates as well as any suggestions for alternative rate methodologies.¹⁵ It asked that parties in disagreement with the proposal offer specific and detailed alternatives.

Opposition to the October 2012 Proposed Reform Options

The proposals for technical and rate changes to the VRS program, while designed to improve the service overall, are not popular with VRS users, who fear that any changes would be to the detriment of the service. Specifically, they argue that the proposed changes would damage the “functional equivalency” of the VRS program. Functional equivalency is a primary element of Title IV of the Americans with Disabilities Act,¹⁶ which requires

telephone transmission services [to] provide the ability for an individual who has a hearing impairment or speech impairment to engage in communication by wire or radio with a hearing individual in a manner that is *functionally equivalent* to the ability of an individual who does not have a hearing impairment or speech impairment to communicate using voice communication services by wire or radio.¹⁷

A number of organizations that represent the deaf and hard-of-hearing community have begun campaigns aimed at stopping any changes to the program, and one website has been created specifically for people to contact the FCC to oppose the changes.¹⁸ In its comments filed on November 14, 2012, the National Association of the Deaf (NAD)¹⁹ summarized the concerns of the deaf and hard-of-hearing community.²⁰

Proposed Changes to VRS Access Technology

The NAD stated in its comments that it believes mandating the use of a single application is not good for deaf and hard-of-hearing consumers. The organization believes that competition among the currently many service providers encourages innovation. Without such competition, the NAD believes that VRS products will not keep pace with technological change. The NAD believes that the FCC should address interoperability problems through third-party testing and product certification. The NAD is also concerned that changes in the technology could pose challenges to some users, making the service less useful.

Proposed Enhancements to the iTRS Database

The NAD did not express any opposition to creating a central iTRS database to keep track of all phone numbers so long as the information is kept private and is well managed.

Proposed Rate Changes

The NAD expressed its concern that rate changes could impede providing functionally equivalent services through VRS. Specifically, it wants the FCC to ensure that cutting reimbursement rates without instituting any minimum quality standards will not decrease service quality. It suggested that the FCC could compensate VRS companies for using nationally certified interpreters or providing a way for users to be better matched with VRS interpreters.

End Notes

¹ TRS is not specifically addressed in this report. TRS is available to the speech impaired and deaf-blind (telebraille). VRS is only for the deaf and hard-of-hearing. Neither the blind nor the speech impaired would benefit from VRS since they would not be able to see the operator or speak to the operator, respectively. Information about the TRS program is available at <http://www.fcc.gov/guides/telecommunications-relay-service-trs>. Information about telebraille is available at <http://www.deafblind.com/telebrl.html>.

² The TRS Fund is similar to another FCC program, the Universal Service Fund (USF). For information on the USF, see CRS Report RL33979, *Universal Service Fund: Background and Options for Reform*, by Angele A. Gilroy.

³ Contributions are made by all carriers who provide interstate services, including, but not limited to, cellular telephone and paging, mobile radio, operator services, personal communications service, access (including subscriber line charges), alternative access and special access, packet-switched, WATS, 800, 900, message telephone service, private line, telex, telegraph, video, satellite, intraLATA, and international and resale services.

⁴ Rolka Loube Saltzer Associates, *Interstate Telecommunications Relay Service Fund Overview*, <http://www.r-l-s-a.com/TRS/>.

⁵ VRS Reform Order, 28 FCC Rcd at 8705-06, paragraph 215.

⁶ See 2015 TRS Rate Filing at 32; 2015 TRS Rate Filing Supplement at 3.

- ⁷ FCC, VRS Overhaul to Improve Phone Service for Americans with Disabilities, CG Docket Nos. 10-51 and 03-123, FCC 13-82, June 7, 2013, paragraphs 1-216, http://hraunfoss.fcc.gov/edocs_public/attachmatch/FCC-13-82A1.pdf.
- ⁸ *Ibid.*
- ⁹ FCC, Structure and Practices of the Video Relay Service Program, CG Docket No. 10-51, and Telecommunications Relay Services and Speech-to-Speech Services for Individuals with Hearing and Speech Disabilities, CG Docket No. 03-123, DA 12-687, April 30, 2012, http://hraunfoss.fcc.gov/edocs_public/attachmatch/DA-12-687A1.pdf.
- ¹⁰ FCC, Structure and Practices of the Video Relay Service Program, and Telecommunications Relay Services and Speech-to-Speech Services for Individuals with Hearing and Speech Disabilities, CG Docket No. 03-123, FCC 11-184, December 15, 2011, http://hraunfoss.fcc.gov/edocs_public/attachmatch/FCC-11-184A1.pdf.
- ¹¹ FCC, Additional Comment Sought on Structure and Practices of the Video Relay Service (VRS) Program and on Proposed VRS Compensation Rates, CG Docket No. 03-123 and CG Docket No. 10-5, DA 12-1644, October 15, 2012, http://hraunfoss.fcc.gov/edocs_public/attachmatch/DA-12-1644A1.pdf.
- ¹² Jeff Rosen, General Counsel, CSDVRS, LLC, letter to Marlene H. Dortch, Secretary, FCC, filed July 10, 2012; Rosen, letter to Dortch, filed August 27, 2012.
- ¹³ Rosen, letter to Dortch, filed May 9, 2012.
- ¹⁴ In general, per §§64.604(c)(5)(iii)(E) and (H) of the commission's rules, the fund administrator is required to file the fund payment formulas and revenue requirements for VRS with the commission on May 1 of each year, to be effective that July 1. However, on April 30, 2012, the FCC waived that obligation, extending interim rates "to remain in effect until the commission completes its review of the compensation method and market structure for VRS." FCC, Telecommunications Relay Services and Speech-to-Speech Services for Individuals with Hearing and Speech Disabilities; Structure and Practices of the Video Relay Service Program, CG Docket Number 10-51 and CG Docket No. 03-123, Order, 27 FCC Rcd 7150, June 26, 2012, http://hraunfoss.fcc.gov/edocs_public/attachmatch/DA-12-996A1.doc.
- ¹⁵ FCC, Additional Comment Sought.
- ¹⁶ 47 U.S.C. §225.
- ¹⁷ 47 U.S.C. §225(a)(1). *Emphasis added.*
- ¹⁸ <http://SaveMyVRS.com>.
- ¹⁹ The NAD was selected for discussion in this report because it is the largest organization representing the interests of the deaf and hard-of-hearing community.
- ²⁰ National Association of the Deaf, "NAD Responds to VRS Public Notice," November 14, 2012, <http://www.nad.org/blogs/andrew-phillips/nad-responds-fcc-vrs-public-notice>.

Chapter 39

SENSORINEURAL HEARING LOSS SECONDARY TO OTITIS MEDIA

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ABSTRACT

Otitis media is an inflammatory condition of the ear, frequently associated to an infection (viral or bacterial). The most frequent type of hearing loss caused by this disease is the conductive, due to effusion in the middle ear and/or erosions of the ossicular chain. Nonetheless, several reports demonstrate sensorineural hearing loss secondary to acute episodes of otitis media, or throughout the course of chronic otitis media. It is the most common infection of the childhood, but the incidence is also high in other age groups. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most frequent bacteria to cause otitis media. The extracranial (e.g., facial nerve paresis, labyrinthitis, mastoiditis, and petrositis), and the suppurative intracranial complications (e.g., brain abscess, epidural abscess, meningitis, hydrocephalus, lateral sinus thrombosis, sinus cavernous thrombosis, subdural abscess/empyema, cerebellitis, labyrinth sclerosis) are the most feared complications of otitis media. Diagnosis is achieved with proper clinical history and examination; audiograms and tympanograms demonstrate and classify the presence and degree of hearing loss. Computed tomography and magnetic resonance imaging could be used during the evaluation of the patients, especially when a complication is suspected. The physiopathologic mechanism leading to the sensorineural hearing loss is the passage of toxins, bacteria, and inflammatory mediators through the round window membrane to the cochlea. Inflammatory damage of the sensory elements in the basal turn of the cochlea has been previously demonstrated in human studies. Antibiotic therapy is the preconized treatment for otitis media, but patients can develop hearing loss even when under adequate treatment. Thus, our objective is to review the concepts of otitis media, focusing on the bacteriology, diagnosis, and to highlight the inflammatory mechanisms leading to the sensorineural hearing loss secondary to this pathology.

INTRODUCTION

Otitis media - a generic term for all types of an inflammatory conditions of the middle ear - is a very common disease among infants and young children. The Eustachian tube is usually shorter and more horizontal in this population, leading to persistent effusion and, frequently, proliferation of bacteria [1]. Although less frequently, otitis media is also considered a common cause of infection in adults and elderly. The effusion and ossicular changes interfere with the sound transmission through the middle ear, causing conductive hearing loss [1]. The hearing loss can lead to impacting consequences, especially in children: auditory deficits often delay the behavioral, educational, and speech development [2, 3]. It is suggested, however, that sensorineural hearing loss can also occur during the course of otitis media [4]. Paparella et al. [5] were the first authors to report sensorineural hearing loss secondary to otitis media. These authors also remark that the severity of sensorineural hearing loss depends on the extent and duration of the infection.

EPIDEMIOLOGY

It is well known that otitis media is the leading cause of antibiotics prescriptions. Furthermore, in developed countries, 80% of the children will experience at least one episode of acute otitis media until their third birthday [6], and 40% will experience 6 or more recurrences by the age of seven [6]. From 1980's to 1990's, the number of visits to the physician's office increased more than 200%, only when considering patients with acute otitis media [3]. Otitis media was the most common diagnosis recorded in 1985, 1989, and 1992 in the United States, and the use of amoxicillin and cephalosporins increased significantly during this period to treat this disease [7].

In the United States, 8.8 million children under the age of 18 years were reported to have ear infections in 2006 [8]. In addition, it is estimated that 65 to 300 million children suffer from chronic suppurative otitis media, causing 60% of them to have associated hearing loss [3]. Furthermore, in 1990, approximately 28.000 childhood deaths were attributed to otitis media [9].

Monasta et al. [6] estimated a global acute otitis media incidence rate (new episodes per hundred people per year) of 10.85%, or 709 million new cases each year. Children under 5 years of age account for 51% of these cases. Also, the authors report the incidence rate of chronic otitis media as 4.76 per thousand people, in a total of 31 million cases; 22.6% of which in children under 5 years of age [6]. The prevalence of hearing impairment due to otitis media was between 2 to 97.04 per ten thousand among the different countries [6]. Conductive or mixed hearing loss due to chronic otitis media have a prevalence of 1.5% [10].

The economic impact of otitis media exceeds \$5 billion dollars annually in the U.S. alone [3, 8]. Mean cost of the treatment of a single episode of otitis media was \$115.80; furthermore, treating one episode of recurrent otitis media was significantly more expensive than treating an initial episode (\$124.64 vs. \$107.81, $P = 0.0001$) [11]. Also, antibiotic use to treat this disease in children is more than three times greater than in any other age group [3]. Finally, each episode of otitis media causes the children to miss, at best, 2 days of school. The

estimated cost of the absences from work of their parents varies between \$300 and \$600 million dollars [12].

Preventive interventions, as well as better access to treatment should be the aim of health policies and programs. Breastfeeding, smoking avoidance, reduction of exposure to indoor and outdoor air pollution are pillars for preventing acute otitis media and its complications and sequelae [6].

BACTERIOLOGY

Both narrow- and broad-spectrum antibiotics have been heavily relied upon for medical management of otitis media. The rate of antibiotic prescription per visit remains about 76-80% [8]. The over-use of antibacterial agents resulted in the emergence of multiple-antibiotic resistant microorganisms, including members of all three genera commonly associated with otitis media.

Young children are in particular risk for otitis media, because of increased viral exposure, naive immunologic system, and impaired Eustachian tube function [8, 13]. Bacteria, viruses, or both were observed in the middle ear fluid in up to 96% of acute otitis media cases [8]. Ruohola et al. [14] reported that, of 79 children subjected to a tympanotomy tube placement, the middle ear fluid contained bacteria and viruses in 66% of the cases; 27% had bacteria alone; and 4% had only viruses.

Substantial data demonstrate the three primary causative agents of otitis media to be *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis* [3]. Vaccines against *S. pneumoniae* and *H. influenzae* are proven to reduce the mortality due to meningitis and pneumonia caused by these agents [6]. Nonetheless, the microbiology has changed over the past 20 years in cases of otitis media [8]. Chronic otitis media cases are also associated with the presence of aerobic bacteria (e.g., *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Proteus mirabilis*, *Klebsiella species*), or anaerobic bacteria (e.g., *Bacteroides*, *Papstotreptococcus*, *Propionibacterium*) [1, 15]. It is important to highlight that antibiotic sensitivity of *P. aeruginosa* or *S. aureus* has changed little in the past few years. However, the antibiotic resistance, specially of *P. aeruginosa* stains to quinolones, has markedly increased [15].

Among the complications of chronic otitis media, we highlight the extracranial suppurative complications (e.g., facial nerve palsy, labyrinthitis, mastoiditis, and petrositis); and the intracranial suppurative complications (e.g., brain abscess, epidural abscess, meningitis, hydrocephalus, lateral sinus thrombosis, sinus cavernous thrombosis, subdural abscess/empyema, cerebellitis, labyrinth sclerosis) [6]. Early diagnosis, including imaging exams of the temporal bone with high definition computed tomography [16], and prompt treatment are crucial to avoid morbid sequels.

DIAGNOSIS

The most common types of otitis media are: acute purulent otitis media, recurrent acute otitis media, otitis media with effusion, and chronic otitis media. Acute otitis media is usually preceded by upper respiratory symptoms, which main clinical symptoms include cough and rhinorrhea [6, 8]. Chronic otitis media is clinically defined as a chronic inflammation of the middle ear and mastoid cavity, with recurrent ear discharges (exudate) or otorrhea through a tympanic membrane perforation, for more than 3 months [1, 6, 17].

There is still some controversy on how to accurately perform a clinical diagnosis of otitis media. Patients with viral infections or other ear diseases are often misdiagnosed as having acute otitis media; furthermore, a proper examination of the eardrum can be hard to perform, especially in uncooperative children, or patients with cerumen occluding the external auditory canal. A study reported that 50% of the patients aged 6 to 35 months with acute otitis media actually met its diagnostic criteria [18]. Table 1 highlights the main criteria used to diagnose each of the most common types of otitis media.

The “red eardrum”, or the ear “with fluid”, should not suggest the diagnosis of acute otitis media unless when associated with bulging of the tympanic membrane or otorrhea, accordingly to the 2013 American Academy of Pediatrics guideline [8]. The appearance of the ear drum evolves over the course of the disease and demands repeated examination. In addition to scrutinizing the color, position, and contour of the tympanic membrane, pneumatic otoscopy or tympanometry could be used to assess the mobility. Absent or reduced mobility, as well as the presence of air-fluid level behind the ear drum, suggest the presence of middle ear effusion [8].

Hearing impairment is the term used to refer to a decrease in the auditory function in the widest possible sense, ranging from barely appreciable impairments to total deafness. According to the World Health Organization, the hearing impairment is classified as: 1- no impairment (25 dB or better in the audiogram); 2- slight (26-40 dB); 3- moderate (41-60 dB); 4- severe (61-80 dB); and 5- profound (81 dB or higher). The mean hearing is calculated separately for each ear as the mean value of hearing in the frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz [10].

Table 1. Criteria for otitis media diagnosis

Term	Definition
Acute otitis media (AOM)	Rapid onset of inflammation of the middle ear -Symptoms include otalgia, irritability, insomnia, anorexia -Signs include fever, otorrhea, full or bulging opaque TM, impaired TM mobility, TM erythema
Recurrent acute otitis media (ROM)	3 or more well-documented and separate AOM episodes in the past 6 months, or ≥ 4 well-documented and separate AOM episodes in the past 12 months with more than 1 episode in the past 6 months
Otitis media with effusion (OME)	Presence of fluid in the middle ear without signs or symptoms of AOM
Chronic otitis media (COM)	OME persisting for ≥ 3 months from the date of onset (if known) or from the date of diagnosis, with a TM perforation

TM = tympanic membrane.

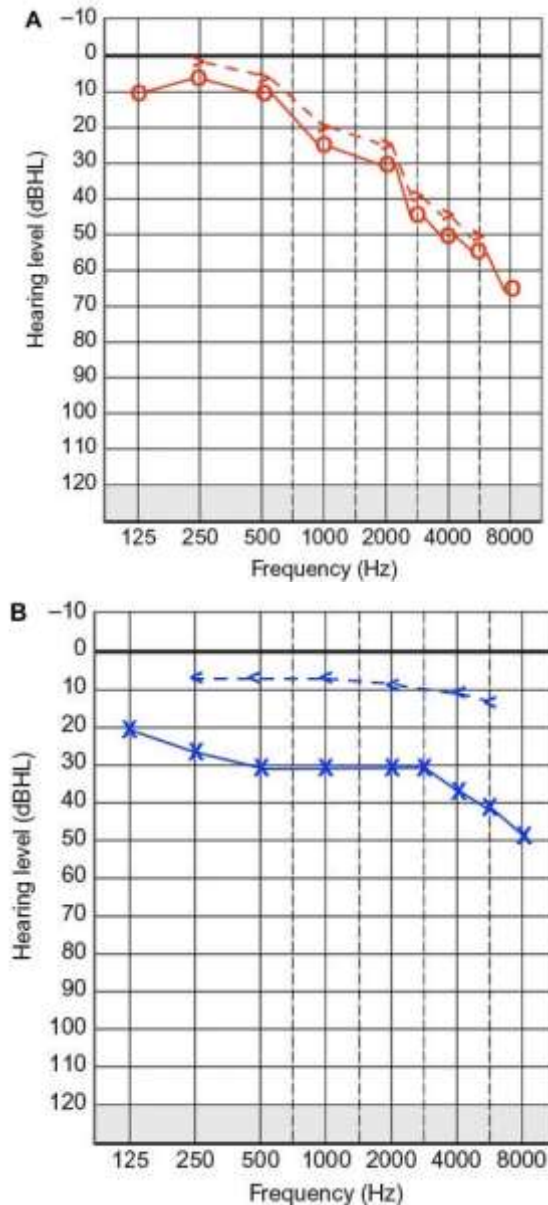


Figure 1. (A) Example of a sensorineural hearing loss in a right ear. The cause lies in the cochlea. Pure-tone audiometry reveals superposable air and bone conduction curves. (B) Example of a conductive hearing loss in a left ear. The cause lies in the external or middle ear. Pure-tone audiometry reveals a difference between the air conduction (X-X-X) and bone conduction (<-<-<) thresholds. Both ears tested with ear and bone loudspeakers.

Both conductive and sensorineural hearing loss were reported among patients with otitis media (Figure 1). Conductive hearing loss usually occur as a result of middle ear effusion, changes in the eardrum or ossicular chain, or secondary to bacterial/viral labyrinthitis [10]. The air-bone gap observed in the audiograms is usually more severe in ears with immobile compared to mobile ossicular chains [19].

High frequency hearing loss has been reported in several studies among children and adults with otitis media. However, the association of the degree of hearing loss with the severity of hearing loss is still under debate [20]. A Korean study with 16.063 participants aged above 20 years old reported a prevalence of chronic otitis media of 3.8%. They also found an odds-ratio to a mild hearing impairment of 1.95 (95% CI, 1.34-2.85), and a moderate hearing impairment of 4.00 (95% CI, 2.21-7.22) in chronic middle ear diseased patients compared to controls.

A population-based cohort that included 32.430 adults (aged 20-56 years) who underwent pure-tone audiometry, tinnitus questionnaire, and physical examination performed by an otolaryngologist, reported that adults with any degree of hearing loss during the childhood were more likely to develop tinnitus in adulthood [22]. A Taiwanese study also reported that patients with chronic otitis media are in significant higher risk of developing sudden sensorineural hearing loss when compared to negative controls [23]. Finally, a Norwegian cohort study, in a 30-year follow-up of 32.786 adults, showed an association between chronic and recurrent otitis media in childhood with the development of hearing loss in adulthood [24].

PHYSIOPATHOLOGY

Chronic otitis media is histopathologically defined as the presence of irreversible tissue pathology in the middle ear [17] (Figure 2). This is a broader definition than the clinical one, in which the presence of perforation in the tympanic membrane is mandatory. Chronic otitis media is usually the final step in the continuum that also include purulent, mucoid, and serous otitis media [17, 25]. Many of its sequelae can result in hearing loss, including (but are not limited to) atelectasis, ossicular erosion or fixation, tympanosclerosis, and presence of abnormal tissue in the ear cleft [25, 26, 27]. These changes can cause conductive hearing loss, due to blockage in the sound transmission mechanisms.

Nonetheless, sensorineural hearing loss, either transient or permanent, is a common feature of the clinical course of patients with chronic otitis media. The hearing loss in the high frequencies seems to be more frequent among these patients, suggesting a structural damage in the basal turn of the cochlea [17, 25, 26]. These assumptions were found to be true in both animal and human studies: the loss of outer and inner hair cells in the basal turn of the cochlea was reported by many authors [26, 28, 29].

These findings led authors to study the interactions between inner and middle ear. Paparella [30] was the first to report these interactions, and many subsequent studies proved that middle ear inflammatory conditions can lead to inner ear damage. There are several possible ways from which the disease could progress towards the inner ear: fistulas (caused by trauma or bone erosion due to cholesteatoma); oval window; and round window. The studies that followed focused in observing the permeability to both oval and round windows to bacteria and other inflammatory products. The permeability of the round window membrane was demonstrated by the induced passage of sodium-22 and horseradish peroxidase through the membrane and into the labyrinth [31]. Goycoolea et al. [32] observed gradual cochlear histopathologic changes followed by obstruction of the Eustachian tube in cats; nonetheless, no changes around the oval window were observed. Goycoolea et al. [33]

reported the passage of traced albumin from the round window niche into the perilymph of the cochlea, suggesting that if such a macromolecule could pass through the membrane, infiltration of smaller particles such as toxins and enzymes could also occur. Following those preliminary studies, several other reports described either passage of substances or recovery of them in the perilymph of the basal cochlear turn: nitric oxide, transgenes, proteins, bacterial exotoxins, antibiotics, local antiseptics, and intact bacteria [34-42] (Figure 3).

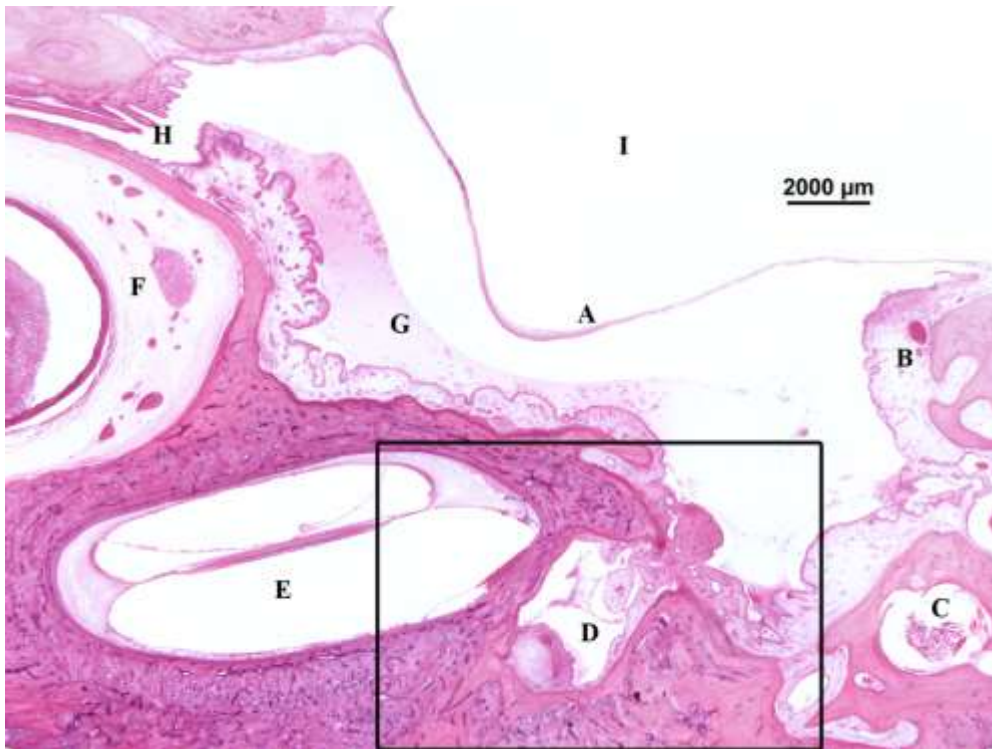


Figure 2. A representative horizontal section of a human temporal bone (2x; hematoxylin & eosin) demonstrating the middle ear cleft and the cochlea in a chronic otitis media case.

A. Tympanic membrane; B. Hyperplastic middle ear mucosa; C. Facial nerve in the Fallopian canal; D. Round window niche; E. Basal turn of the cochlea; F. Carotid artery; G. Serous-purulent effusion in the middle ear cleft; H. Eustachian tube; I. External ear canal. Square: Round window niche and early basal turn areas.

The death of bacteria resulting from immune response and/or antibiotic treatment releases inflammatory products in the middle ear cleft, such as lipopolysaccharide, peptidoglycan, and DNA [43]. These products exacerbate and prolong inflammation in the middle ear [43-45]. In the acute otitis media, the most expressed inflammatory cytokines include tumor necrosis factor (TNF)- α , interleukin (IL)-8, and IL-1 β [44, 45]. In chronic otitis media, prolonged inflammation increases the risk of tissue destruction and remodeling. MacArthur et al. [46] further observed greater cytokine expression in the middle ear of rats with acute otitis media when compared to the non-diseased contralateral side. These cytokines not only create a persistent inflammatory state in the inner ear, but also affect the ion-homeostasis receptors, such as aquaporins and ATPase ion pumps. In a situation of a chronic inflammation, down-regulation of these mechanisms could increase extracellular fluid accumulation, leading to

more severe damage. Trune et al. [47] also observed, in both acute and chronic otitis media, increased expression of genes responsible for connective tissue reorganization (matrix metalloproteinase - MMP), neovascularization (MMP, and fibroblast growth factor - FGF), and bone restructuring (bone morphogenetic protein - BMP). Those genes could be responsible for the tissue remodeling and pathologic changes in ears with chronic otitis media.

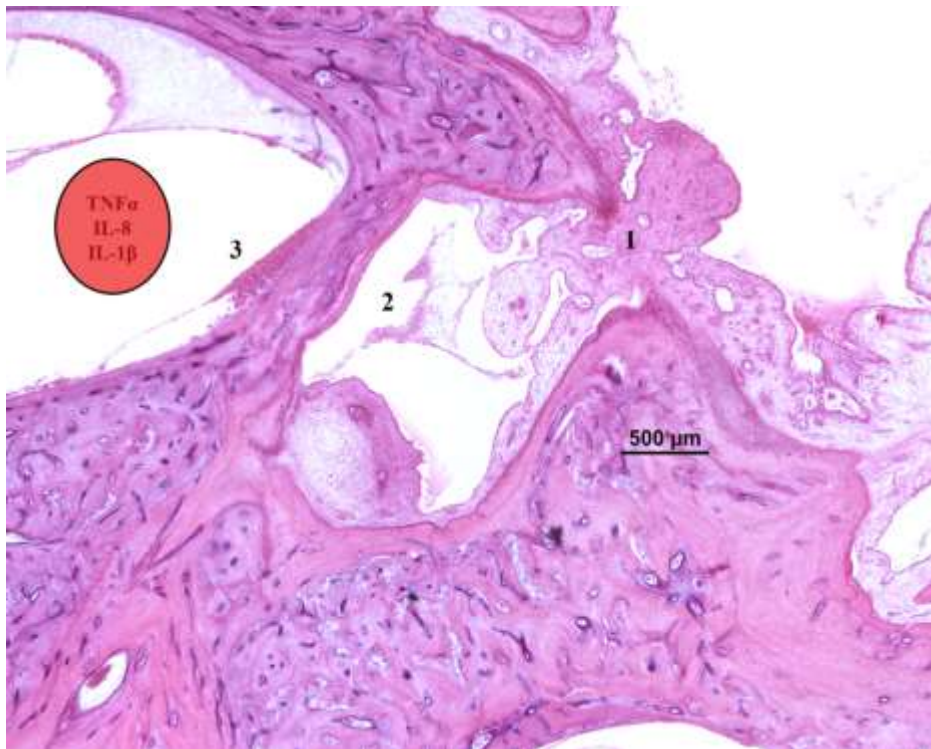


Figure 3. A representative horizontal section of a human temporal bone (4x; hematoxylin & eosin) demonstrating the round window niche and the early basal turn of the cochlea; this picture represents the squared area from figure 2 seen under a higher magnification. This picture represents the infiltration of the cochlea (inner ear) by inflammatory products.

1. Hyperplastic mucosa and granulation tissue blocking the round window niche; 2. Inflammatory cells in the round window niche; 3. Inflammatory cells in the basal turn of the cochlea; TNF-alpha: Tumor necrosis factor alpha; IL: Interleukin.

Regarding the histopathologic changes in human temporal bones, Meyerhoff et al. [48] described labyrinthitis, inflammatory cells infiltrating the round window membrane, and cochlear hydrops. Loss of inner and outer hair cells in the basal turn of the cochlea is another marked characteristic feature of the disease; the loss of hair cells is observed even when comparing the diseased to the non-diseased contralateral side in the same patient. Joglekar et al. [31] found a 39% loss of outer hair cells in chronic otitis media temporal bones, versus 9.7% in non-diseased controls; similar changes were observed in the inner hair cells (22% of loss in the diseased cases versus 3% in the controls). The authors also reported a decrease in the volume of the stria vascularis in the basal turn in the otitis group, but no differences in the

spiral ligament was observed. These findings are responsible for the sensorineural hearing loss in high frequencies observed in chronic otitis media patients.

CONCLUSION

The sensorineural hearing loss is a potentially morbid consequence of otitis media, especially in children. Associated factors such as duration and severity of disease, recurrent infections, and permeability of the round window membrane are directly related to the degree of sensorineural hearing loss. Correct diagnosis, treatment, and counseling of patients with otitis media is mandatory to prevent possible sequels.

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Chapter 40

SUDDEN SENSORINEURAL HEARING LOSS: PATHOPHYSIOLOGY, DIAGNOSIS, TREATMENT OPTIONS, AND PROGNOSTIC FACTORS

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ABSTRACT

Introduction: Sudden sensorineural hearing loss (or sudden deafness) is characterized as a new onset of unilateral or bilateral hearing loss, in which the symptoms develop within 24-72 h. Estimates of the annual incidence of sudden sensory hearing loss range from 5-30 cases per 100,000 people. Audiometry of these patients show a loss of 20-30 dB in at least three connected frequencies.

Review of the literature: Many theories have been proposed to explain the cause of this disease: inflammatory reaction (viral infection of the labyrinth or cochlear nerve), vascular disturbances, autoimmunity, rupture of the membranes, or decreased oxygen flow to the inner ear. Diagnosing the cause of sudden deafness involves a detailed clinical history, audiological, biochemical, vestibular, and imaging tests. The hearing impairment should always be considered as secondary to a specific cause; nonetheless, most cases are classified as idiopathic. The identifiable causes of the sudden deafness include: Infectious diseases, trauma, autoimmune diseases, ototoxic drugs, changes in blood flow, tumors in the vestibulocochlear nerve, neurologic diseases, and inner ear disorders (such as Meniere's Disease). Magnetic resonance imaging is considered the gold standard imaging exam to detect lesions in the inner ear structures, internal auditory canal, and cerebellopontine angle. Since the majority of the cases are idiopathic, the treatment of these cases is essentially empirical. The decision whether to treat or not to treat idiopathic cases is also controversial, since some studies state that 20-65% of the patients recover the hearing spontaneously without any treatment. Furthermore, no drug has been proven to significantly improve the prognosis of the hearing loss in the idiopathic cases. Based on the proposed pathophysiology, some treatments are described in the literature, including: corticosteroids, vasodilators, carbogen, intratympanic dexamethasone,

hyperbaric oxygen, vitamins, ginkgo biloba extract, and stellate ganglion blockers. If the hearing loss is permanent, hearing aids could be beneficial. The presence of associated vertigo, the severity of hearing loss, the pattern shown in the audiogram, time between onset and treatment, and hearing loss in the contra-lateral ear, when present, indicate worse prognosis. Including tinnitus in the list of prognostic factors is considered controversial, since it is present in about 80% of the cases of sudden deafness.

Conclusion: The symptoms of sudden deafness should be promptly recognized, and the search for a possible cause is imperative. Correct diagnosis and treatment could prevent the hearing changes from being permanent.

INTRODUCTION

The first definition of sudden sensorineural hearing loss (SSNHL) was proposed by Kleyen [1]: a rapid-onset hearing loss, which characteristic audiometric finding is sensorineural hearing loss of 30 dB or more over at least three contiguous audiometric frequencies. The symptoms are usually acute, developing over a period of a few hours to days.

The estimated yearly incidence of SSNHL is 5 to 20 cases per 100,000 people. The disease often leads to permanent hearing disability, accounting for about 1% of all sensorineural hearing losses [2, 3].

The etiology and pathology of SSNHL is still under debate. The main point of discussion is the difficulty to find the exact cause of the symptoms: a background cause can be found in only 10% to 15% of the cases, as suggested by histopathologic studies of human temporal bones [4-9].

Several theories have been proposed for explaining the etiology of this disease, including viral infections, circulatory disorders, rupture of the inner ear membranes, immune disorders, metabolic, and toxic causes [4-9]. However, although defeatist, idiopathic SSNHL is still a very frequent diagnosis [7].

PATHOGENESIS

There are several theories trying to explain the pathologic mechanisms leading to SSNHL, none of which universally accepted. Among the main theories, we describe in detail the viral, vascular, autoimmune, membrane rupture, and toxicity theories.

Viral Theory

Several studies indicate viral infection as one of the most common etiologic factors; the high incidence of upper respiratory tract infection (30-40%) prior to the symptoms add further support to this theory. There is even evidence correlating concomitant seasonal aspects of the incidence of respiratory infections and SSNHL [10-12].

Many viruses have been postulated as possible causes of sudden sensorineural hearing loss, including mumps (7% of adult cases) [13], varicella-zoster, rubella, cytomegalovirus, Epstein-Barr, adenovirus, and influenza [12].

There are two mechanisms proposed to explain how a viral infection can cause SSNHL: (1) contamination of the fluid spaces and soft tissues of the cochlea, which cause inflammation, or invasion of the cochlear nerve (neuritis) [14], reaching the inner ear either via bloodstream or directly from the middle ear, passing through the round window membrane [15, 16]; and (2) reactivation of latent viruses within tissues of the inner ear, since it has been observed that neurotropic viruses can remain dormant in the cochlear neurons [14, 17].

Histopathological findings also add support to the viral theory, since the reported changes are quite similar to what found in cases of sensorineural hearing loss secondary to viral infections and idiopathic labyrinthitis [14, 17-19]. The temporal bones had several cochleosaccular abnormalities, including collapse of the organ of Corti (Figure 1), loss of cochlear hair cells, atrophy of the tectorial membrane, atrophy of the stria vascularis (Figure 2), decrease in the number of spiral ganglion cells, collapse of the saccular membrane and partial absence of the sensory epithelial layer in the saccular macula [14, 17-19].

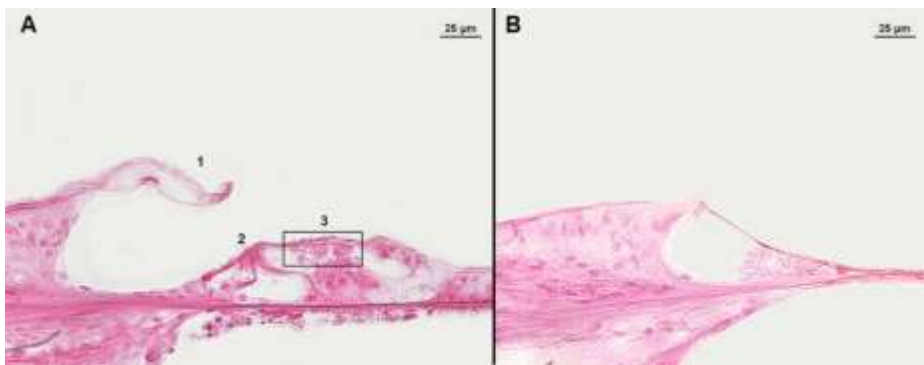


Figure 1. Two representative horizontal section of a human temporal bone, showing the organ of Corti in the scala media of the cochlea (hematoxylin and eosin; 40x). A = a well preserved specimen, with an intact organ of Corti; B = complete collapse of the organ of Corti. 1 = tectorial membrane; 2 = inner hair cell; 3 = three columns of outer hair cells.

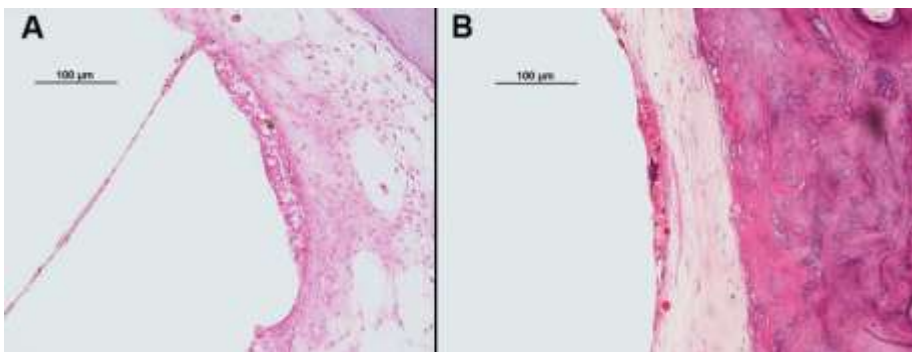


Figure 2. Two representative horizontal sections of a human temporal bone, showing the stria vascularis in the scala media (hematoxylin and eosin; 20x). A normal stria vascularis; B = atrophy of the stria vascularis.

Vascular Theory

Some studies investigated several possible vascular mechanisms leading to SSNHL, and these include thromboembolic events, vasoconstriction, hypotension, blood hyper viscosity, and atherosclerosis. Factors as excessive weight, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, diabetes mellitus, and smoking habits have consistently been more frequently found in patients with SSNHL than in non-diseased control patients [20].

Igarashi et al. [20] reported cochlear fibrosis and ossification in the inner ear, suggesting necrosis of the membranous labyrinth after vascular occlusion. They also suggest that the inner ear may be more vulnerable to ischemia within the vertebrobasilar system than the vestibular and cochlear nerves. Evidence found in magnetic resonance imaging (MRI) demonstrate that peripheral vestibular disorders in elderly patients were frequently associated with decrease in the rate of the blood flow to the vertebrobasilar system [21-23].

More recently, some authors have investigated the relationship between SSNHL and stroke [24, 25], and they suggested that SSNHL could be an early signs of stroke (such as the “sentinel headaches” in the occasion of subarachnoid hemorrhages) [24]. Lee et al. [24] reported, in a cohort study, that 4 out of 12 patients with SSNHL had stroke (all of them in the irrigation territory of the anterior-inferior cerebellar artery (AICA)) within the first 2 months after the onset of the hearing loss. Furthermore, Lin et al. [25], in a cohort including more than 1400 patients with SSNHL, concluded that these patients had, after adjusting for other factors, 1.64-times (95% confidence interval, 1.31-2.07; $P < 0.001$) more chances of having a stroke within the 5-year follow-up period when compared to controls. These results add further support to the vascular theory for the SSNHL.

Autoimmunity Theory

Sudden hearing loss can be the first clinical manifestation of several known and suspected autoimmune diseases. The theory of autoimmunity as the cause of the hearing loss is supported by several findings, including decreased number of circulating lymphocytes CD3+, CD4+, and CD8+ [26], greater presence of antibodies against smooth muscles, and a lack of anti-thyroid and antinuclear antibodies [27-29]. Furthermore, it has been described several changes in human temporal bones of donors who had autoimmune diseases when alive, such as degeneration of the organ of Corti (Figure 1), stria vascularis (Figure 2), and spiral ganglion [14].

Experiments also demonstrated the existence of a local immune response within the inner ear from immunocompetent cell recruitment in the endolymphatic sac from the blood stream [30]. The presence of increased anticardiolipin antibodies was also reported, but the pathologic mechanism of this finding is still under debate: either the autoimmunity could cause direct lesion to the cochlear elements, or the anticardiolipin antibodies can cause micro thrombosis in the inner ear small vessels, further supporting the vascular theory [30].

The hearing loss diagnosis of autoimmune origin comes from established criteria. Major criteria include: (1) bilateral involvement; (2) systemic autoimmune disease; (3) high levels of ANAs, (4) reduced number of naive T cells (CD4+ RA); and (5) high rate of hearing recovery (above 80%). Minor criteria are defined as (1) unilateral involvement; (2) young or middle-

aged patients; (3) serum reactivity against HSP-70; and (4) positive response to steroid treatment but with small to no recovery of the hearing levels.

Membrane Rupture Theory

In 1971, a report of perilymphatic fistulae was reported as a cause of SSNHL. Surgical findings have been described since then, demonstrating fistulae on round, oval, or both labyrinthine windows [31]. Nonetheless, until today, the theory of perilymphatic fistulae as cause of vestibular or cochlear symptoms is still controversial [32].

Simmons [33] reported a few cases of hearing loss secondary to mechanical disruption of inner ear membranes. The author suggested a double membrane break theory for idiopathic SSNH (both in oval and round windows), leading to pressure changes between the endolymph and perilymph compartments. Furthermore, Stroud and Calcaterra [34] suggested that these fistulae could occur even without any history of trauma or past surgeries. Thus, the authors hypothesized that spontaneous labyrinthine window ruptures could be one of the factors included in the etiology of SSNHL.

The relationships with cerebrospinal fluid pressure changes and perilymphatic spaces were explored and showed pathways between cochlear aqueduct and scala tympani, and between internal auditory meatus and scala vestibule. The labyrinth, with its delicately balanced perilymph-endolymph system, is surrounded by delicate membranes that present intimate relations to hydrodynamic forces in the carotid arterial system, the intracranial venous-sinus systems and forces in the subarachnoid space. When a membrane break occurs near the vestibule, both audition and balance are disturbed because system's membrane is nearly connected with the cochlea.

Toxicity Theory

Some medications are also implicated in the occurrence of SSNHL, including amikacin, vancomycin, erythromycin, cisplatin and others [35]. The mechanism is similar to the ototoxic causes of long-term sensorineural hearing losses [36], and the degree, severity, and time between the use of the drug and the symptoms depend on several factors, including the thickness of the round window membrane (for topical medications) [37], and the presence of melanin pigment particles in the inner ear elements (for both topical and systemic drugs) [38].

DIAGNOSIS

The diagnosis of SSNHL must be faced as the starting point of the investigation rather than an end. When a specific cause is found, timely and correct treatment can decrease (or even prevent) the incidence of permanent hearing impairment.

SSNHL should be suspected when the patient complains of a sudden decrease in the hearing in one of the ears. Detailed clinical history should include how long before the consult the symptoms began; progression (sudden or delayed); severity of hearing loss;

laterality of SSNHL; and associated symptoms, such as vertigo, tinnitus, aural fullness, otalgia or neurological deficits [39, 40]. Physical examination is essential to exclude other causes of sudden hearing loss, such as impacted cerumen, otitis media, or tumors affecting the middle-ear [41]. A careful otoscopy, associated with Weber and Rinne tests (using a 512-Hz tuning fork) [42] are enough to exclude other causes of hearing loss, plus further suggesting the sensorineural cause of the impairment.

Furthermore, investigation should always include urgent auditory assessment, preferentially with vocal and pure tone audiometry (including both bone and air conduction thresholds) – the presence of sensorineural hearing loss of 30 dB or more over at least three contiguous audiometric frequencies is diagnostic [42]. Speech discrimination score, tympanometry test, and study of the presence of stapedial reflex are also helpful and provide further information to the attending physician. Schreiber et al. [41] (2010) advocate that, if sensorineural hearing loss is confirmed by audiometry, an oto-neurological examination should be performed to evaluate central or peripheral vestibular disorders as demyelination, inner-ear dysfunction, pontine angle-lesions or posterior circulation abnormalities.

The degree of hearing impairment can be classified accordingly to the level of the loss observed in the audiometry, graded in decibels (dB): (1) Mild: loss of 26-40dB; (2) moderate: 41-70dB; (3) severe: 71-90dB; and (4) profound: loss of more than 90 dB [41, 43, 44]. Other authors also suggest a different classification: mild (15 or 20-40 dB), moderate (40-60 dB), severe (60-80 dB), profound (80-100 dB), and total hearing loss (>100 dB) [45, 46]. Even though the literature demonstrate that the degree of hearing impairment due to SSNHL is variable, it is usually classified as moderate to profound [45, 47, 48].

Regarding diagnostic testing, the brainstem evoked response audiometry (BERA) is considered to be a useful test to suggest the presence of retro-cochlear lesions that could be the cause of the SSNHL [49]. Although this test is very sensitive in suggesting these lesions, it lacks specificity. Furthermore, the MRI constitutes a very reliable imaging exam: it demonstrates the presence or absence of inflammatory labyrinthitis, vascular disorders, or lesions involving specific areas of the cerebellopontine angle, brain, or brainstem [21, 49, 50].

Even though it is suggested that the MRI should be performed in the moment of the SSNHL diagnosis [50], other authors recommend the MRI to be performed only when BERA suggest retro-cochlear lesions [22]. The most frequent finding in the MRI is enhancement of the labyrinth; the enhancement usually occurs due to neoplastic or inflammatory lesions, such as autoimmune or viral disorders [49, 50]. Decreased vertebrobasilar flow and lacunar infarcts, showing as areas of high-intensity signal, are also frequently found in the MRIs of these patients [22, 43]. Mark et al. [49], in MRI studies of 12 cases of SSNHL, observed that all the patients had signs of enhancement of the labyrinth in the affected side. Ramos et al. [50] reported, in a study involving 49 patients with SSNHL, a 46.9% of MRI changes, including labyrinth enhancement, tumors at the cerebellopontine angle, and vascular disorders.

Patients with several cardiovascular risk factors, especially the elderly, should be subjected to a magnetic resonance angiogram (MRA); this exam is considered the gold standard to evaluate the presence and degree of obstruction of arteries that could lead to SSNHL [21, 22, 43, 44, 51, 24, 52]. The AICA is the main vessel supplying the labyrinth; thus, infarction of the territory irrigated by this artery is commonly associated with vestibular symptoms, including vertigo, tinnitus and hearing loss [43, 24]. Other possible causes for the SSNHL that should be investigated include infectious (syphilis, HIV, cytomegalovirus

[CMV], meningitis), autoimmune, trauma, and neurological diseases [11], as well as the use of ototoxic medication [41, 51]. Laboratory investigation should include hemogram, blood glucose, five-hour blood glucose test, cholesterol and lipid profile, clotting factors, VDRL, FTA, C-reactive protein, erythrocyte sedimentation rate, antinuclear and anticardiolipin antibodies, lupus anticoagulant, and antineutrophil cytoplasmic antibodies. Assessment can also include viral serology for herpes simplex types I and II, varicella zoster, Epstein-Barr virus (EBV), CMV, HIV and mumps virus [41, 53, 54].

TREATMENT

All of the treatment options for SSNHL are still controversial, since 65% patients achieve spontaneous recovery to normal levels of hearing [48]. Furthermore, one of the most debated questions when dealing with a patient with a suspected SSNHL is, if treatment with drugs is indicated, when to ideally introduce the medications.

Ideally, the treatment should be focused towards the specific cause of the SSNHL. As the screening process leading to the exact cause of SSNHL remains a challenge, treatment in the acute phase is mostly empirical. Thus, in literature some authors propose therapies in the acute phase that could treat all possible etiologies – that strategy is usually referred to as “shotgun therapy” [51].

Anti-Inflammatory Treatment

Oral corticosteroids are widely used to treat SSNHL, but further evidence of the beneficial effect in these patients is still needed [41, 55-58]. Furthermore, a meta-analysis failed to demonstrate differences in the outcomes of the SSNHL when comparing steroid to other treatment options (including anti-virals, carbogens, or other vasoactive agents) [57].

Nonetheless, systemic steroids seem to prevent inner ear damage during several inflammatory, infectious and immune-mediated conditions [6, 48, 57, 59]; furthermore, MacArthur et al. [59] demonstrated that steroid can prevent inner ear damage during infectious middle ear diseases in an animal model. The optimal dose of oral or intravenous corticosteroids has not yet been determined [48]. Chen et al. [48], in a ten-year retrospective analysis, observed that treatment with oral corticosteroids had a significant impact in the recovery rate of patients with severe hearing loss, but not on those with mild to severe hearing loss. The absence of effect in the mild to severe group might be due to the higher rate of spontaneous recovery in these patients; recovery rate in the untreated group was 53%. Oral corticosteroid treatment is usually performed for 10-14 days; prednisone is the most frequently prescribed steroid, in a dose 1 mg/kg/day or a maximum of 60 mg, followed by a taper of 10 mg every 2 days [42].

Recently, intra-tympanic dexamethasone (ITD) has been proposed as an additional therapy to the conventional modalities, due to the possibility of avoiding the systemic collateral effects of the steroids, plus reaching higher concentration in the perilymph. The main mechanism for this modality is based on the semi-permeable nature of the round window membrane, which allow the penetration of the medication in the inner ear

compartments [15, 16, 37, 42, 60, 61]. In a prospective, randomized, and controlled clinical study [60], 30 patients were treated with ITD plus systemic steroids, and 30 only received systemic steroids. No significant benefit effect of the ITDs in the overall hearing was observed; nonetheless, the hearing level at the frequency of 250Hz significantly improved in the ITD group. On the other hand, Ho et al. [61] found contrasting results: patients with severe to profound SSNHL that received ITD therapy (4 mg/ml, 0.4-0.7 ml, once a week for 3 weeks) after failure of the standard treatment had significantly higher rates of hearing recovery when compared to a non-ITD group. Furthermore, the authors consider ITD to be an alternative for patients in which systemic steroids have failed. The optimal dose for ITD must be better investigated.

Therapy to Increase Cochlear Blood Flow (CBF)

Since vascular etiology is one of the theories for the genesis of sudden deafness, many treatments have been proposed in an attempt to improve CBF, including vasodilators (histamine, verapamil, carbon dioxide, papaverine hydrochloride) or drugs that decrease blood viscosity (dextran, batroxobin, pentoxifylline).

Carbogen inhalation (composed of 5% carbon dioxide and 95% oxygen) is used for treating SSNHL based on its vasodilator effect. Fish et al. [27] demonstrated that the pressure of carbon dioxide (PCO_2) has a stronger stimulation in cochlear blood flow than pressure of oxygen (PO_2) only, and PO_2 and PCO_2 are intensely influenced by hyperventilation, hypoventilation or apnea, since these conditions affect the oxygen tension in the perilymphatic compartments. The author also demonstrated that carbogen achieved higher increments in cochlear oxygenation than 100% O_2 or air + 7% CO_2 . When comparing carbogen with other vasodilators (papaverine and dextran IV), he found that carbogen inhalation had better hearing recovery than vasodilators when re-evaluated 1 year following treatment. Nevertheless, the use and beneficial effects of the carbogen inhalation are still considered to be controversial [56].

Defibrogenation therapy with batroxobin is another proposed treatment for sudden deafness [62]. It has been reported that this drug reduces blood viscosity, with better results in hearing improvement and other associated symptoms when compared to systemic steroids. Kubo et al. [62] (1988) found better improvement in the hearing levels in the batroxobin when compared to the bethametasone group. On the other hand, Cinamon et al. [56] found no difference between the use of batroxobin and steroids.

Ginkgo biloba has also been described to have good benefits since it contains flavones and terpenes, which acts avoiding the formation of free-oxygen radicals, controlling vessel contraction [63]. In patients with uncomplicated SSNHL, high dosages of the extract EGb 761 proved to be beneficial (240 mg per day for 8 weeks) [64].

Pentoxifylline is also described as an agent capable of improving CBF by reducing the blood viscosity. It inhibits platelet aggregation and rises flexibility of erythrocytes and leukocytes. Also, a decrease in the hematocrit results in increasing oxygen tension, by improving the inner ear perfusion [56]. Reisser and Weidauer [63] compared the hearing improvement between Ginkgo biloba extract EGb 761 (200 mg daily, for 10 days) with pentoxifylline (300 mg daily for 10 days) and found that both therapies are effective; however, the ginkgo biloba had better outcomes when considering the tinnitus as well.

Anti-Viral Therapy

To our knowledge, there is no strong scientific evidence that supports the use of antivirals [57, 58], in spite of the data supporting a viral cause in histopathologic studies in humans' temporal bones [14, 19, 65].

Shotgun Therapy

A study suggested a standardized treatment for SSNHL, named as the “Belgium cocktail” [66]. The proposed drug regimen for these patients is as follows:

- steroids: prednisolone 1 mg/kg;
- piracetam: 3 x 3 1200 mg/day (10.8 g/day)
- vitamin E: 2x 600 IU/day
- magnesium: 167 mg/day
- acyclovir: 5x 800 mg/day for 7 days (only when the patient presents within the first 3 days of the onset of symptoms).

Even though this empirical treatment modality includes a very schematic therapy for the acute phase of the SSNHL, to our knowledge, no further randomized, double-blind studies were performed to validate the efficacy of this treatment compared to placebo.

Other Treatment Modalities

Following the assumption that a decrease in the cochlear blood flow could result in hypoxia, some authors hypothesized that therapies which could increase oxygen tension could be beneficial for these patients. In an attempt to prove this hypothesis, several treatments have been proposed. Hyperbaric oxygen therapy (HBO) has been used to increase oxygen tension in inner ear circulation, perilymph and endolymph. In this treatment, the patient inhales, through a mask, oxygen at a 100% level, under 2.5 atmospheres, once a day. Each session lasts 90 minutes [67]. Aslan et al. [67], in a retrospective chart review, observed that patients who underwent treatment HBO associated to the conventional steroid treatment had better recovery of hearing, especially in the first 2 weeks of the onset and in younger patients (less than 49 years old). They reported that advanced age has a negative influence in the recovery of sudden deafness, probably due to microvascular disturbances present in the elderly. The authors finally conclude that HBO therapy is recommended in patients with less than 50 years old. In addition, elderly population should not be subjected to HBO therapy due to possible and serious complications.

Some authors advocate the use of vitamins to treat SSNHL, based on the hypothesis that they could reduce oxygen-free radicals, protecting the sensorial elements of the cochlea against cellular damage [47]. These authors reported better hearing outcomes in patients using vitamin E associated with steroids when compared to patients using steroids in monotherapy.

In addition to the treatment, patients with unilateral SSNHL should also be carefully oriented in order to minimize the risk of hearing loss in the good ear [42] (Rauch et al., 2008). It is recommended for these patients to use noise protection devices (such as earplugs) to avoid acoustic trauma, and avoid scuba diving or activities involving sudden pressure changes. The patients should also be oriented to search an otolaryngologist immediately if new or recurrent symptoms present.

PROGNOSIS

Many studies dedicated to assessing the prognosis of the hearing loss secondary to SSNHL. The prognosis depends on several factors, including (but not limited to): demographics, etiology, disease process, duration, audiogram characteristics, and impact on cochlear and vestibular structures [5, 68]. In untreated patients, 65% completely recover the hearing levels spontaneously, in about 14 days [10]. However, in some patients, the hearing levels will not improve at all [30].

The disease onset age was most important demographic factor to act in the prognosis of the SSNHL: patients older than 60 had decreased rates of hearing recovery, and lower absolute threshold gains [5, 51].

The shape of the hearing loss in the audiogram are also intimately associated with the prognosis: patients with low-frequency or mild-frequency hearing losses achieve better final auditory results when comparing to those with flat or downsloping hearing loss [4, 5, 10].

Patients who present for evaluation within a week after the onset of the first symptoms have higher chances of hearing recovery; furthermore, the probability of complete recover is also higher when compared to those who presents after the first 7 days. Thus, the chances of hearing recovery gradually decrease over time [5, 69]. Although these findings might suggest that early treatment improve the chances of better hearing outcomes, this assumption has not been supported by other following studies [5, 14, 69]. Concomitant imbalance or vertigo is also associated to poorer recovery of the hearing levels [5]. Furthermore, patients with abnormalities on electronystagmography also had worse chances of recovery when compared to those without those abnormalities [51, 69].

CONCLUSION

SSNHL should be promptly recognized, and the search for a possible cause is imperative. Correct diagnosis and treatment could prevent the hearing changes from being permanent.

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Chapter 41

UP-TO-DATE IN AUDITORY NEUROPATHY SPECTRUM DISORDER: CLINICAL, DIAGNOSTIC AND THERAPEUTIC FEATURES

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ABSTRACT

Auditory neuropathy spectrum disorder is a condition in which there is a change in the neuronal transmission of the auditory stimuli, due to the involvement of inner hair cells of the organ of Corti or involvement of auditory nerve synapses. It is characterized by the absence or alteration of waves in the brainstem auditory evoked potentials exams.

Medical literature shows a great variability in findings related to auditory neuropathy, both in its etiology and epidemiological data. About 80 pathogenic mutations have been described in individuals with non-syndromic deafness, with an emphasis on the GJB2 and p.Q829X mutations.

Clinical diagnosis may vary in several degrees with unilateral or bilateral hearing loss (symmetrically or not), a low speech discrimination (incompatible with audiometric thresholds), fluctuating hearing levels, presence of otoacoustic emissions and cochlear microphonic detection, with no auditory brainstem responses.

Cochlear implantation or fitting of hearing aids should be performed as early as possible for a better hearing rehabilitation.

In this upcoming chapter we intend to present the epidemiological features, clinical presentation, genetic findings, and treatment options for patients experiencing auditory neuropathy spectrum disorder.

INTRODUCTION

Auditory neuropathy term was first used in 1996, and during the Conference of Consensus on Auditory Neuropathy/Dyssynchrony in Como, Italy (2008) [1], it was changed to auditory neuropathy spectrum disorder due to many clinical forms of this particular disease.

The auditory neuropathy spectrum disorder (AN) is a disease believed to be a sensory disturbance of the inner ear on its interface with the brain stem and/or in the auditory cortex, and it is observed a deficient neural activity of the cochlear nerve, and further related to injuries that can affect the inner hair cell synapse, spiral ganglion, axon, the myelin sheath, and the nerve dendrite [2-5].

Many groups studying this entity still disagree with the diagnoses parameters as well as with the treatment, mainly because several situations and circumstances in which the diagnostic tools are insufficient to properly diagnose it. Anyway, the classical findings are the presence of otoacoustic emissions and an absence of response in the auditory brainstem response [1].

The basic treatment consists in speech and language therapy with auditory training, supported by conventional hearing aids or cochlear implantation, when necessary [4].

This chapter will briefly review all current data available about this disorder and highlight the clinical presentation, and treatment options for this entity.

EPIDEMIOLOGY

Hearing loss is the most prevalent sensory disorder in humans. It may be caused by a combination of several factors, as environmental (exposure to frequent high-intensity sounds, acoustic trauma, infections and ototoxic drugs), or genetic factors [6]. In developed countries, more than 60% of all cases of hearing loss result from genetic causes [7]. International statistics show one case of hearing loss in every 1,000 births. In Brazil, however, environmental factors outweigh those of genetic origin, and the frequency of hearing loss is estimated at four per 1,000 births, but depending on the sample and studied area, it may be present in 2-7 per 1,000 newborns [6].

Auditory neuropathy is an auditory disturbance in which the function of the outer hair cells of the organ of Corti is normal, but the function of the inner hair cells is compromised. This condition may affect any subject at any age group, with a prevalence between 0.23 to 2% of the children [5]. It is believed that about 8% of all new annual cases of hearing loss are related to AN. A recent study found a prevalence of 1.2% of AN among 2,292 patients with hearing loss [8], and Manchaiah et al. showed that patients with AN have an association with hereditary neurological disorders in 42% of the cases; toxic, metabolic, immunological, and infectious disorders in 10% of the cases; and unknown cause in 48% of the cases [9].

The large number of genes expressed in the cochlea reflects the complexity of the molecular mechanisms involved in this organ [10]. Most cases of hereditary hearing loss are non-syndromic (70%, approximately). When autosomal dominant, they are named as DFNA; autosomal recessive as DFNB, X-linked (X-DFN), or mitochondrial [6]. It is estimated that 75-80% of cases of non-syndromic genetic deafness are autosomal recessive, 20-25% are

autosomal dominant, and 1-2% are X-linked. The mitochondrial inheritance is estimated at 1% [11].

DIAGNOSTIC

Auditory neuropathy is a type of sensorineural hearing loss (Figure 1) known with auditory stimulus alteration as a result of the involvement of inner hair cells or auditory nerve synapses. The absence or alteration of the waves in the auditory brainstem response test and the presence of otoacoustic emissions (Figure 2) and/or cochlear microphonism is characteristic of this disease [12]. Furthermore, a normal otoscopy, absence of middle ear disease, absence of speech recognition threshold, absence of acoustic reflex, and imaging examination (computed tomography and magnetic resonance imaging) showing the presence of the cochlear nerve and excluding other retrocochlear pathologies are mandatory.

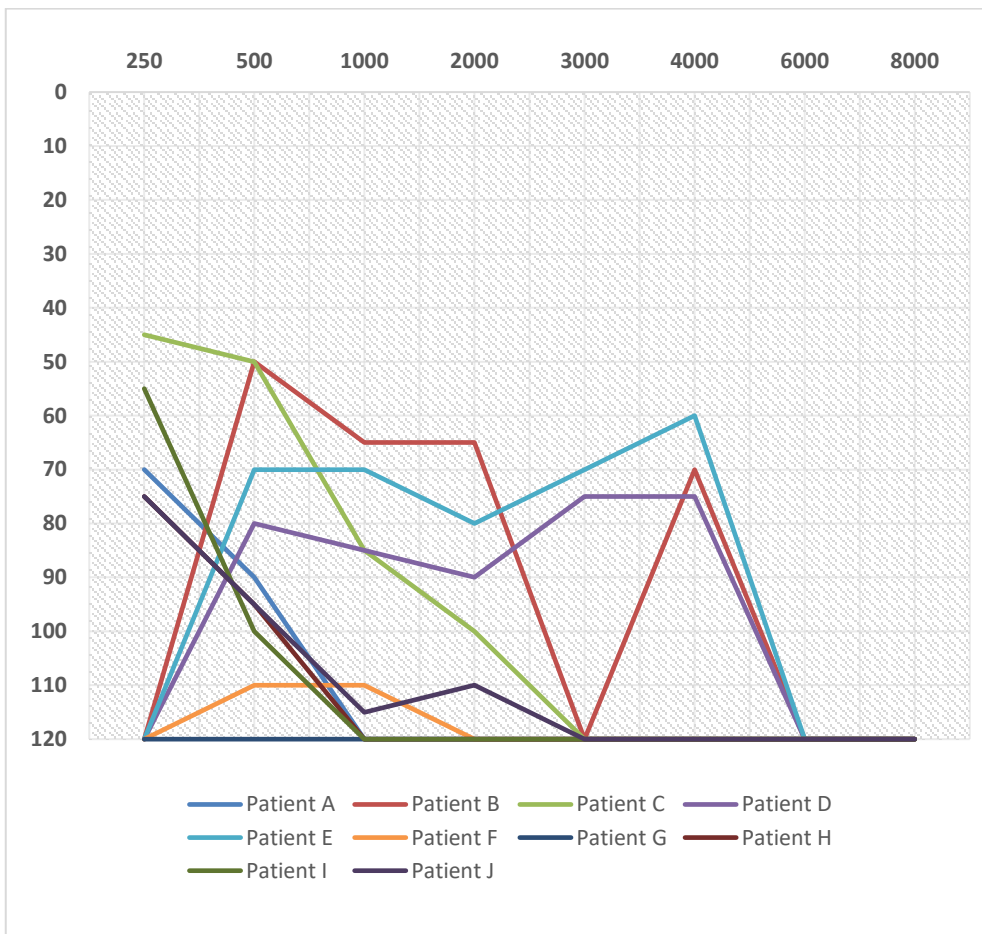


Figure 1. Examples of sensorineural hearing loss caused by auditory neuropathy spectrum disorder.

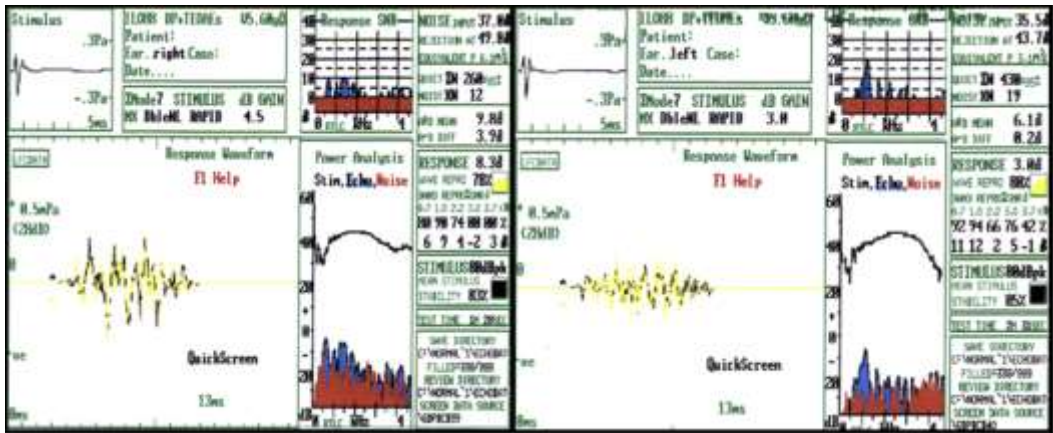


Figure 2. Examples of present otoacoustic emissions in a case with no ABR response.

It is related to 7 to 10% of the cases of hearing loss in children, and can be caused by genetic factors, or environmental factors, such as hyperbilirubinemia, prematurity, anoxia, exposure to ototoxic drugs, infections, and others [13]. When considering the syndromic association, AN can be related to systemic neurodegenerative diseases, such as Charcot-Marie-Tooth disease, Friedreich's ataxia, Guillain-Barré neuropathy, and others [7].

Considering the genetic factors, we can mention that otoferlin (*OTOF*) gene – located in the locus DFNB9, chromosomal region 2p22-23 – is one of the 40 genes associated to autosomal recessive non-syndromic hearing loss, and is expressed in the cochlea, vestibule, and brain [14]. Another gene, diaphanous-3 (*DIAPH3*) – located in the locus *AUNA1*, chromosomal region 13q21-q24 – was identified in 2004 and it is associated with autosomal dominant postlingual AN [15]. The *PJVK* gene – located in the locus DFNB59, region 2q31.1-q31.3 – encodes pejvakin, a protein of the afferent auditory pathway involved in signaling form hair cells and neurons [16]. Additionally, mutations in connexin 26, the gap junction $\beta 2$ (*GJB2*) gene, are also associated with AN [8]. However, it is not clear how the mutations in the *GJB2* gene may cause changes in the inner hair cells and nerve endings of the hair cells, but Carvalho et al. identified homozygous c.35delG deletions in patients with AN using polymerase chain reaction (PCR) method [6].

Lastly, AN associated with mitochondrial disease may be related to hereditary syndromes as mentioned before, including Charcot-Marie-Tooth disease, Leber's hereditary optic neuropathy, autosomal dominant optic atrophy, autosomal recessive optic atrophy, Friedreich's ataxia, Mohr-Tranebjaerg syndrome, and Refsum's disease. Mitochondrial mutations are especially related to aminoglycoside-induced hearing loss and maternally inherited non-syndromic hearing loss (with no exposition to aminoglycoside). Mitochondrial mutations, like m.1095T > C (in the mitochondrial 12S rRNA gene), and m.1555A > G (in the *MTRNR1* gene) are examples of these mutations [17].

REHABILITATION

The degree of hearing loss in patients with AN varies from moderate to severe, and treatment is a special challenge for otolaryngologists and speech therapists, since the audiometric thresholds tends to fluctuate, as well as the measurements of speech performance [18]. In the past, AN patients were treated in different ways, ranging from a simple observation, to the use of hearing aids (Figure 3) and frequency modulation system, with poor results predominantly.

As conventional treatment for AN has been shown refractory to conventional amplification, cochlear implantation rises as an alternative therapy for this condition. Cochlear implantation has a large evidence for treatment of various forms of hearing loss. It has also been demonstrated that earlier fitting of cochlear implants in children with hearing loss leads to an important speech development [19]. At the same time, the data available about cochlear implantation in patients with AN all over the world has shown different results, probably because this entity is so heterogeneous and has so many possible etiologies [1].

Despite this fact, several cochlear implantation groups indicate this procedure to patients with AN who do not have a considerable improvement with speech therapy and the use of hearing aids.

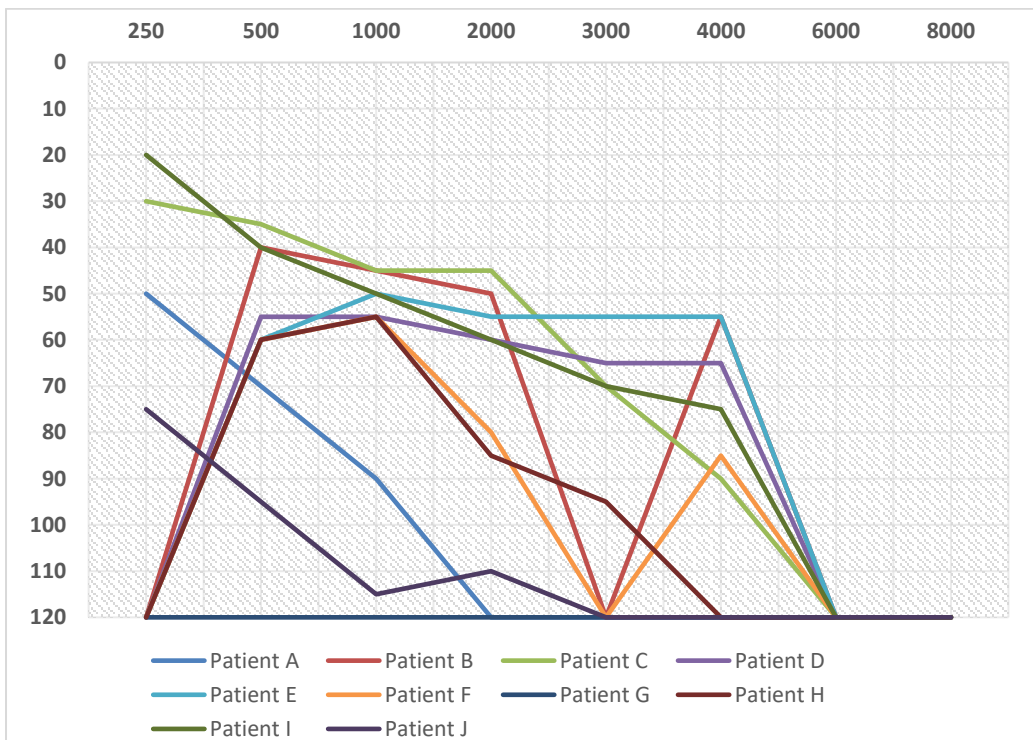


Figure 3. Examples of patients mentioned in Figure 1 fitted with hearing aids.

CONCLUSION

Auditory neuropathy spectrum disorder is a very heterogeneous clinical situation. The diagnosis is not clear and the treatment stills a challenge. It is necessary to use of all the resources for a detailed diagnosis, establish a clear relationship with the patient and their families, individualize each case and focus on a hearing rehabilitation, speech development and speech processing, and interpretation of auditory stimuli and sound information by any ways.

Speech therapy, cochlear implant, auditory training, and hearing aids are the main therapeutic options and they can be combined to achieve better results.

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Chapter 42

GENETIC KIDNEY DISEASES WITH SENSORINEURAL HEARING LOSS

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ABSTRACT

Kidney diseases does not commonly curse with hearing loss. However, there are several groups of genetic diseases who progress to chronic kidney disease and they curse with symptoms of bilateral progressive sensorineural hearing loss.

The most typical example of these diseases is Alport syndrome. This is a group of diseases caused by mutations in COL4A3, COL4A4 or COL4A5 genes. These genes encode $\alpha 3$, $\alpha 4$ and $\alpha 5$ chains of collagen IV. This kind of collagen is located in the glomerular basement membrane, inner ear and eye.

Alport syndrome shows different forms of inheritance (autosomal dominant, autosomal recessive or X-linked), but all of them cause haematuria, proteinuria and progressive chronic renal failure, which evolves until the need for renal replacement therapy. This renal involvement is accompanied by ocular manifestations as lenticonus or maculopathy and high tones progressive bilateral sensorineural hearing loss, which is a key symptom of the syndrome.

Another group of genetic diseases with hearing impairment is caused by different mutations in the MYH9 gene. This gene encodes nonmuscle, myosin heavy chain II-A (nmMHC-IIA). Their mutations cause different disorders with an autosomal dominant inheritance, presenting with macrothrombocytopenia with giant platelets and leukocyte inclusion bodies (set of symptoms known as May-Hegglin anomaly), with or without deafness, nephropathy and cataracts. These syndromes, formerly known as Fechtner or Epstein Syndrome, are now called MYH9-Related Disorders.

1. INTRODUCTION

Renal diseases, which can evolve to chronic kidney disease with the need of a treatment with dialysis or kidney transplantation, are not usually related to sensorineural hearing loss.

Nevertheless, there are two groups of genetic diseases who typically combine, between many other features, sensorineural hearing loss and certain kidney injuries which, finally, evolve towards chronic kidney disease [1, 2]. These diseases are caused by mutations in several genes: those who codify the type IV collagenous chains (whose mutations provoke variants of Alport syndrome) and the gen who codifies heavy chain of non-muscle myosin IIA (mutations in this gene generate MYH9 related disorders).

In this chapter we will do a brief summary of these two groups of diseases, to explain their physiopathology, clinical features, diagnostic and treatment, focushing on the hearing injuries.

Finally we will explain the relationship between sensorineural hearing loss and chronic kidney disease treated with haemodialysis. Although this topic escapes from the general aim of this chapter, we find interesting to explain the possible relation between hearing loss and kidney disease in an effort to better understand the physiopathology that relates these two disorders.

2. HEARING LOSS AND ALPORT SYNDROME

Alport syndrome (AS) includes a group of hereditary diseases caused by mutations in the COL4A3, COL4A4 or COL4A5 genes. These genes are responsible for the biosynthesis of $\alpha 3$, $\alpha 4$ and $\alpha 5$ collagen IV chains, which are located in the glomerular basement membrane of the kidney, the inner ear and the eye [3].

AS has three different patterns of inheritance, which generate three different entities: AS associated to the X chromosome (OMIM 301050) in 80% of the cases, caused by mutations in COL4A5 gene, autosomal recessive AS (OMIM 203780), which is caused by homozygous mutations in COL4A3 or COL4A4 genes, and it appears in 15% of the cases; and autosomal dominant AS (OMIM 104200), which is the result of heterozygous mutations in COL4A3 or COL4A4 genes and it is diagnoses in the remaining 5% of the patients (Figure 1). In all of them, mutations of the corresponding genes prevent the production or the proper type IV collagen network, which generates the clinical expression of the disease [1, 3]. So, the main symptom is haematuria, which progresses to chronic renal failure and dialysis.

The most frequent ocular symptom is anterior lenticonus, which generates a special myopia that requires frequent changes of corrective lenses [4].

Introduction

The typical hearing impairment in AS is sensorineural bilateral hearing loss [2], with variable intensities, progressive and symmetrical, affecting middle and high frequencies.

It is a key symptom for the diagnosis of AS in haematuric nephropathies, because its presence in these cases is highly suggestive of this genetic disorder.

Although there are studies who show a prevalence of 55% in men and 45% in women [4], the real prevalence is unknown, since many patients do not undergo routine audiometries [1, 3].

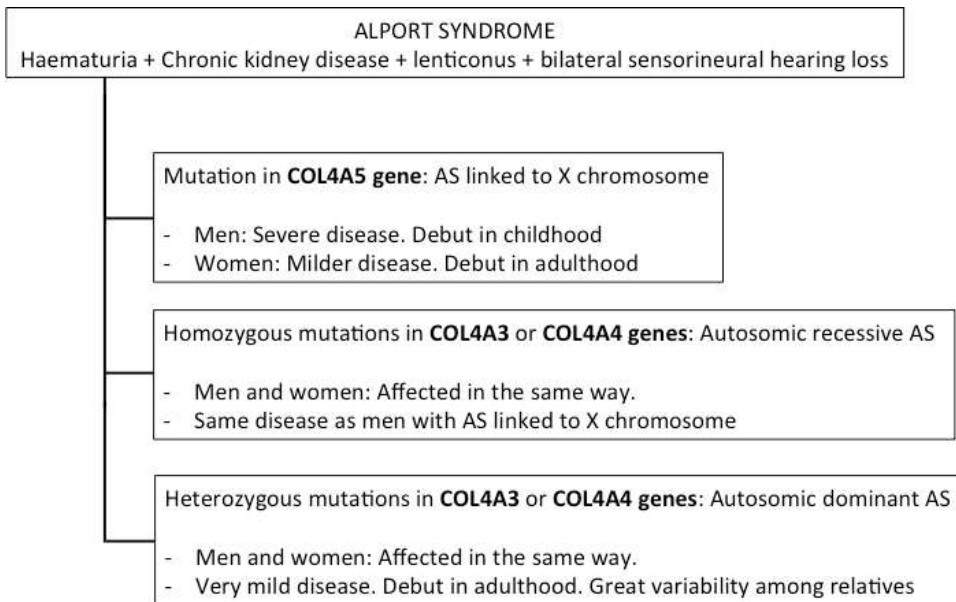


Figure 1. Different modes of inheritance and clinical expression of Alport syndrome. C. Rosado, ENT & audiology news 2015.

Physiopathology

Type IV collagen basal membranes are the main constituents of membranous labyrinth [5, 6]. One of the possible role of these collagen chains is the active adjustment of basilar and tectorial membranes, a essential stage in the discrimination of frequencies and amplification of auditory signs [7, 8].

The phsiopathological hypothesis is that the injured synthesis of type IV collagen generates the defective adhesion of the Corti's organ to the basilar membrane [7].

Our knowledge of the physiopathology of hearing loss in AS come to us especially from the study of experimental animal models, since studies in human ears are restricted because of different thecnical difficulties.

These animal models show us the existence of different injuries, like:

- Thinning of cochlear basal membrane, which may have some effect on the rigidity of the membrane [8].
- Affection of stria vascularis, with edema in endothelial cells and reduction of the internal diameter of capillaries [8]. These facts may restrict the blood flow through the metabolically hyperactive tissue.

- Absence of $\alpha 3$, $\alpha 4$ and $\alpha 5$ chains in spiral ligament [9], which could result in a reduced capacity of myofibroblasts to maintain enough tension in the basilar membrane, with loss of perception for high sounds.

Clinic

Hearing loss is one of the first signs of AS, but it is not congenital, because it is detected for the first time during the late childhood or in the early adolescence in male patients with AS associated to the X chromosome, and by the 40 years of age, 80-90% of the male patients have developed it. However, in some families, deafness is not detected until later stages of life. The reason for these differences on the age of debut and the clinical evolution is that both factors are related to the kind of mutation [10].

In women affected by AS associated to the X chromosome, hearing loss is less common, and it usually appears on a later stage, because only 18% of female patients are affected at 15 years old, compared to 85% of men, and at 40 years old, only 45% of the female patients are affected [2, 3].

There does not seem to be any difference regarding to sex in the incidence of clinical evolution of the autosomal forms. In patients with autosomal recessive AS, hearing loss appears at a young age, but in the autosomal dominant cases, it can develop later in life, although these patients show a great clinical variability.

In its initial stages, the auditory deficiency can only be detected with an audiometry, which shows a bilateral decrease in sensitivity to 2000-8000 Hz range tones. This hearing loss is progressive and spreads to other frequencies, including those in the conversational range, and it can be incapacitating by the second decade of life [10].

Regarding the audiometry, a study revealed three different audiometric configurations: ascending curve in 47.1% of the patients, descending curve in 41.2% and flat curve in 11.7% of the cases. The mean of thresholds in 500, 1000 and 2000 Hz was 33dB HL in flat curve; 42 dB HL in ascending curve and 50 dB HL in descending curve. Flat curve was seen at the age of 8.5 years; ascending at 13.7 years and descending at 17.8 years, which could suggest a progression of the curve.

The fact that hearing loss is one of the first and most typical signs of Alport syndrome is very useful in the study of patients with haematuria. Because of this, there are some particular patients, like these ones with haematuria lacking familiar record (the novo mutations) [4], or when performing a kidney biopsy is not possible, the discovery of a sensorineural bilateral hearing loss suggests, in a very clear way, the diagnosis of AS.

On the other hand, we should include the study of urinary sediment in the diagnosis of all hearing losses with this form of clinical presentation.

Different methods for auditory assessment, like audiometry, auditory brainstem responses and otoacoustic emissions, should be employed in the research of the index case and the other family cases (affected and asymptomatic) to investigate all disease holders [10].

Traditionally it had been stated that bilateral sensorineural hearing loss was always accompanied by renal failure, although it could start before the appearance of end-stage chronic kidney disease, since the hearing impairment is not related to uremia, but it is the result of an injury in cochlear basal membranes [4].

Hearing loss would run parallel to the progression of the renal failure, and this fact would suggest a poor renal prognosis.

This idea has been recently challenged, since a new mutation has been described in the COL4A3 gene, in a family with autosomal dominant AS. This mutation is C.345 delG, which generates a frameshift (pG115GfsX37), whose result is a truncated $\alpha 3(\text{IV})$ collagen chain that produces an impaired collagen network. Some members of the affected family, who carry the mutation has bilateral sensorineural hearing loss as the single manifestation of the disease, while other relatives have all the symptoms of the disease. This fact confirms that hearing loss is an independent symptom of the AS, it is not linked to the renal impairment and it does not indicate the prognosis of kidney disease [3, 6].

It has not still be determined the reasons for the great variability of the clinical course of deafness in different patients. Several hypotheses have been proposed, such as the kind of mutation (frameshift and nonsenses would generate the most aggressive hearing loss), or the influence of other proteins which interact with the collagen IV network, but more studies are necessary to explain this point [3].

Treatment

There is no special treatment for this kind of hearing loss, unless the hearing aid or cochlear implant when the deafness is so severe that it diminishes the patient's quality of life. The early diagnosis of Alport syndrome, with or without genetic diagnosis does not allow us to use any therapeutic measure to stop or slow the course of deafness.

The progress of the disease leads to the need of dialysis and, eventually of a kidney transplantation. These treatments can worse the hearing function, since haemodialysis generates osmotic and electrolytic affections in endolymph, and several drugs used as immunosuppressants in kidney transplantation, like cyclosporine A and corticoids) cause affection to viscosity of plasma and circulation of inner ear [10].

These facts carry us to conclude that patients should benefit of a regular follow up and a careful rehabilitation of hearing during the curse of the illness.

Some authors reported stabilization or even slower progression of hearing loss in post-transplantation patients, but others have not observe that possitive evolution, but a worsening [10]. Because of these contradictory and conflicting observations, more studies are needed for the complete understand of evolution of hearing loss after the kidney transplantation.

There is a rare but severe complication of renal transplantation in patients with Alport syndrome, which is the development of anti-MBG nephritis (a kind of Goodpasture syndrome). This complication is more frecuent in a particular profile of patients: men with hearing loss and end-stage renal failure before the age of 30 years [5]. Hearing loss assessment may contribute to create this risk profile in order to anticipate the developement of this complication.

Conclusion

As a conclusion, we can state that sensorineural bilateral hearing loss is a key feature in the diagnosis of the all types of AS. Audiometry is an essential diagnostic test that must be

included in the study of haematuria, mainly if there is a strong suspicion of a genetic disease. There is no relationship between the pattern of inheritance and its severity nor with the development of chronic kidney disease.

3. HEARING LOSS AND MYH9-RELATED DISORDERS

MYH9 related disorders (MYH9RD) are a group of autosomal, dominantly inherited disorders caused by mutations of MYH9, which encodes the nonmuscle myosin heavy chain IIA (NMMHC-IIA) [12].

Non-muscle myosins II are members of the myosin superfamily of motor proteins. NMMHC-IIA is a heavy chain which is part of the Non-muscle myosin IIA. This protein is encoded by the MYH9 gene, which is located on chromosome 22q12–13 and comprises 44 exons, 40 of which contain the coding sequence. It is expressed in many different tissues, including platelets, leukocytes, kidney, and cochlea [12, 13].

Between its functions are maintaining the cytoskeleton and regulating cell adhesion, cell migration, and cell division (cellular processes in which force and translocation are necessary). It is also the end point for the convergence of several signalling pathways.

Each NMMHC-IIA contains two regions: a globular one at the amino terminus, that catalyses ATP hydrolysis and binds to actin to generate force and movement, and an alpha-helical carboxy-terminal tail region, which facilitate the assembly of bipolar filaments [13].

MYH9 mutations are associated with several clinical entities, which are: May–Hegglin anomaly (OMIM 155100), Sebastian syndrome (OMIM 606249), Fechtner syndrome (OMIM 153640) and Epstein syndrome (OMIM 153650). Some years ago, all these entities were considered different illnesses but, after the discovery of MYH9 gene and its mutations, all of these disorders have been included under the name “MYH9 related disorders” [12].

MYH9RD has been diagnosed worldwide and there is no evidence of variation in prevalence across ethnic populations. Although it is considered a very rare disease (for instance, the Italian Registry for MYH9RD includes only 180 affected Italians), the actual prevalence is expected to be higher, since mild forms are discovered incidentally and severe forms are often misdiagnosed as other disorders.

MYH9RD is characterized by a complex phenotype. The main feature is macrothrombocytopenia, which is present in all disorders included in this illness. The difference lies in the presence of the other clinical symptoms, which include basophilic Döhle-like bodies in neutrophils, progressive nephropathy with haematuria and proteinuria, sensorineural hearing loss, presenile cataracts, and glomerulopathy [14].

Table 1. Clinical and laboratory findings in MYH9RD

	May–Hegglin	Sebastian	Fechtner	Epstein
Macrothrombocytopenia	+	+	+	+
Döhle-like bodies	+	+	+	-
Hearing loss	-	-	+	+
Cataracts	-	-	+	-
Kidney disease	-	-	+	+

May–Hegglin anomaly and Sebastian syndrome are characterized by thrombocytopenia, giant platelets, and granulocyte cytoplasmic inclusion bodies, called Döhle-like inclusion bodies, without further organ involvement. Fechtner syndrome has also sensorineural hearing loss, progressive glomerulopathy, and presenile cataracts. Epstein syndrome is characterized by macrothrombocytopenia, hearing loss, and glomerulopathy but Döhle-like bodies or cataracts are absent [13].

Symptoms such as hearing loss, glomerulopathy and cataracts may develop many years after the diagnosis of macrothrombocytopenia, and so, the diagnosis of idiopathic chronic thrombocytopenia is done, delaying the correct diagnosis. This problem is heightened in sporadic cases lacking a family history [12, 13].

Introduction

Sensorineural hearing loss is the most frequent extra-hematological, noncongenital manifestation of the MYH9RD. It has been reported in 60% of patients and in 36–71% of pedigrees. In many individuals it progresses to severe and profound deafness with high impact on quality of life. It is a key symptom in the differential diagnosis of chronic macrothrombocytopenia [15].

Physiopathology

The pathogenesis of this kind of hearing loss remains unclear, since we only have animal studies. Studies on mouse inner ear showed MYH9 immunoreactivity in various cochlear tissues, including hair cells, the spiral ligament, and the Reissner membrane, and no immunoreactivity was found in the auditory neurons or within the stria vascularis. Further studies have indicated that mutant NMMHC-IIA may cause hearing loss by affecting hair cell dysfunction through structural and/or functional disruption of its stereocilia, plasma membrane, and/or mitochondria [16]. These findings could be extrapolated to the humans after the verification of some successful treatments with cochlear implants.

Nevertheless, studies in humans remain necessary in order to completely understand the physiopathology of this kind of hearing loss.

Clinic

The expressiveness of the hearing impairment is heterogeneous. The variable phenotypic expression is observable not only between families but also within families having the same mutation.

The general way of expression is that this kind of hearing loss is a bilateral sensorineural defect that, at the onset or in mild forms, is evident only for high tones, but it progresses towards severe to profound deafness involving also middle and low frequencies.

The onset of the defect is distributed in a homogeneous way from the first to sixth decade. When it begins in childhood or adolescence, the progression is severe and leads to deafness by the age of 30 years [13].

Data from the literature show us that 36% of patients develop hearing loss before age 20 years, 33% between ages 20 and 40 years, and 31% after age 40 years. Once diagnosed, hearing loss frequently progresses over time, although it remains stable in a minority of patients. In 90% of patients with an abnormal audiometry, hearing loss interferes with normal activities [17].

The severity of hearing impairment is variable among different patients; some of them suffers from a mild or moderate defect, even in the elderly, but in other cases, hearing loss presents during childhood and progresses to profound deafness within the first decades of life, which generates a great disability for them [13].

Several genotype-phenotype studies have shown that mutations in the globular, amino terminus domain have a higher risk of early-onset and severe deafness than subjects with mutations in the tail region.

Another fact that may explique the great variability genotype-phenotype is the joint effect of specific mutations and environmental factors, as well as multiple gene products, such as polymorphic protein variants interacting with MYH9 [15], but these hypothesis must be confirmed in further studies.

Treatment

Although there is not a definitive treatment for the illness, the early diagnosis is important, in order to establish an early vigilance and treatment of some symptoms. Thrombopoietin mimetics can control bleeding tendency due to thrombocytopenia, and angiotensin receptor blockers and/or angiotensin-converting enzyme inhibitors are used to minimize proteinuria [14]. Nevertheless, this early diagnosis is often difficult and it depends on physician awareness of MYH9RD.

There is not any definitive treatment which delay de progression of hearing loss. At present, the only recommendation is to avoid ototoxic factors like some drugs or heavy noises.

Drugs like aminoglycosides, salicylates in large quantities, loop diuretics and some chemotherapy regimens should be avoided or be used only after a careful assessment of the risks versus the benefits.

If noise exposure cannot be avoided (like in some jobs), the use of ear devices, like headphones, to attenuate intense sound is necessary.

When the hearing loss evolves to a high degree, these patients are potential candidates for cochlear implantation. Until recent dates, no consistent data were available about the risk to benefit ratio of this intervention in MYH9RD patients with severe to profound deafness. But recent case reports and case series show us that it is safe and effective in most of these patients and should be offered to them as soon as they develop the criteria for candidacy [16].

These studies reveal us that the results of the intervention is similarly good in patients with different total durations of deafness and with different ages at implantation (childhood up to eight decade). The outcome is also similar regarding the specific MYH9 injury or the place of mutation in the protein.

We should think about certain particular aspects of this disease when programming a cochlear implant, like reduced platelet counts, that results in an increased risk of bleeding complications during or after surgery and the delayed wound healing.

The co-operation of the hematologist is required to assure the establishment of preventive measures, like prophylactic transfusion of apheresis platelet concentrates in cases with severe thrombocytopenia or the routinely use of tranexamic acid when the thrombocytopenia is moderate [12].

Another problem in these patients can be the increased risk of infection after the surgery; which is not uncommon among MYH9RD patients, due to, for instance, the immunosuppressive treatment after kidney transplantation [17].

Nevertheless, we can assume the cochlear implant as a safe procedure in MYH9RD whenever adequate prophylactic interventions are carried out.

Conclusion

Hearing loss observed in MYH9RD is the most frequent symptom after the thrombocytopenia. It is bilateral and It can evolve up to the complete loss of hearing. It is a key symptom to distinguish these diseases from other kind of thrombocytopathies.

The cochlear implant can be an optimal treatment for these patients.

4. HEARING LOSS AND CHRONIC KIDNEY DISEASE

Recent studies have revealed an important relationship between chronic kidney disease of any etiology and the prevalence of sensorineural hearing loss, in the form of a mild degree sensorineural hypoacusis in patients undergoing haemodialysis [1, 2].

The prevalence, degree, and patterns of this hearing loss associated with chronic kidney disease differ significantly. Some data say that up to one third of patients undergoing haemodialysis experiences some degree of hearing impairment. The great part of them suffer from mild hearing loss, which can affect both high and low frequencies, although the involvement of high frequencies might be the most common audiometric abnormality in chronic kidney disease affected patients.

These studies show us that this kind of hearing loss is more obvious in the elderly and in patients who have received fewer haemodialysis sessions. We can then state that hearing loss may be inversely associated with the number of haemodialysis sessions but not with duration of disease [18].

The physiopathogenic mechanism of this association remains unclear, but the antigenic similarity between basement membranes of glomeruli and stria vascularis of the inner ear may be an important fact. Some other harmful factors can be the use of ototoxic drugs (it is very important in these patients), electrolyte disturbances and arterial hypertension [2].

The role of haemodialysis in the hearing loss of patients with chronic kidney disease remains unclear, since several studies have produced contradictory results, with a great number of them reporting that haemodialysis plays no role in this association, but a recent work demonstrated that the greater the duration of disease, the greater the hearing loss [18]. Thus, despite the great amount of studies regarding hearing loss in CKD, unanswered questions remain regarding the role of haemodialysis and duration of the disease.

For these reasons, well-designed studies with larger sample sizes are needed to elucidate the causal relationships between hearing loss in chronic kidney disease and haemodialysis.

This association makes us also wonder for the usefulness of the generalized screening for sensorineural hearing loss in patients affected by chronic kidney disease, or, at least in patients receiving haemodialysis, in order to instaurate an early treatment.

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Chapter 43

STEPWISE APPROACH TO THE DIAGNOSIS OF HEARING LOSS IN CHILDREN

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ABSTRACT

Hearing loss in children can be congenital or acquired. It can be classified in prenatal, perinatal and postnatal, considering the time of occurrence, and it can be transitory or permanent. The worldwide estimated prevalence of hearing loss is 1/1000 for children without risk factors for hearing disease, 2-3/100 for those with risk factors. The prevalence of prelingual hearing loss in Italy is reported in 0.7/1000 within the Italian population [1].

The early detection of hearing loss, as well as the early appropriate intervention, is critical for a proper language, relational and cognitive development. Therefore, Universal Neonatal Hearing Screening (UNHS) programs have been developed with the intention of detecting neonatal hearing loss. UNHS consists in testing TEOAEs (transient evoked otoacoustic emissions) eventually followed by ABR (Auditory Brainstem Response), when the registration of TEOAEs fails or when there are risk factors for hearing loss. Nevertheless, not all forms of hearing loss can be identified through UNHS: children with a late onset or a progressive hearing loss can have a delayed diagnosis due to the initial negative result at the UNHS. Therefore, it has been recommended to consider with particular attention all these children and to establish a tight audiological follow up since the first year of life. A careful diagnostic work-up of hearing loss is necessary in order to establish the etiological classification and, thus, the most appropriate treatment. This multidisciplinary and stepwise approach can involve audiologists, otolaryngologists, pediatricians, geneticists, ophthalmologists, maxillofacial surgeons, neurologists, radiologists [2]. History taking and physical exam are the first steps in the assessment of hearing disorders in children. Audiometric tests are fundamental to evaluate the type and the degree of the hearing loss. Also genetic and radiologic evaluations are always recommended for a better assessment of hearing loss. Finally, laboratory and serological

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tests as well as electrocardiogram, ophthalmologic evaluation, kidney and thyroid ultrasound and function tests could give important information in order to exclude infections or syndromes associated to hearing dysfunction [3].

INTRODUCTION

Hearing loss in children can be congenital or acquired. It can be classified in prenatal, perinatal and postnatal, considering the time of occurrence, and it can be transitory or permanent. There are many possible causes of hearing loss in children, even if sometimes the etiology remains unknown. It is always important to recognize as soon as possible the presence of hearing impairment in children, in order to ensure the best possibilities to correct the hearing function and, thus, to allow the develop of the best communicative, relational, linguistic and cognitive performances.

Aim of this chapter is to describe the stepwise approach to the diagnosis of hearing loss in children in order to establish, when possible, the etiology of hearing loss and, also, the most appropriate treatment.

EPIDEMIOLOGY AND ETIOPATHOGENESIS

The worldwide prevalence of hearing loss in children is estimated in 1/1000 among children without risk factors, and 2-3/100 within children with risk factors for hearing loss. The prevalence of prelingual hearing loss in Italy is reported in 0.7/1000 [1].

There are many possible causes of hearing loss in children, and these can be congenital or acquired. Hearing loss can be classified in prenatal, perinatal and postnatal, considering the time of occurrence, and it can be transitory or permanent.

In 2007, the Joint Committee on Infant Hearing indicated the risk factors associated with permanent, congenital, delayed-onset or progressive sensorineural hearing loss (SNHL) in children [4]. In particular, a positive familiar history of hearing loss is an undeniable risk factor for both prenatal and postnatal hearing impairment. Infants admitted to the Neonatal Intensive Care Unit (NICU) for more than 5 days or underwent an exchange transfusion for hyperbilirubinemia (in any case when total serum bilirubin is >25 mg/dL, or when it is above the exchange level, differently calculated depending on the hyperbilirubinemia risk factors and the hours/days of life of children [5]) or an assisted mechanical ventilation or an Extra Corporeal Membrane Oxygenation are considered at risk for a SNHL until the first years of life [6]. Among congenital hearing loss in children, about 40% is genetic and the transmission modalities can be autosomal recessive, autosomal dominant, X-linked or mitochondrial. To date, more than 120 genes linked to hearing loss have been identified. In the 70% of genetic forms, hearing loss is isolated; in the remaining 30%, it can be associated to other malformations (i.e., cardiac, cerebral, ocular), configuring a syndromic form [7, 8, 9, 10].

In children, more than 50% of non-syndromic autosomal recessive SNHL and about 40% of sporadic cases are linked to a characteristic mutation of connexin 26 (Cx26 or GJB2) gene. These congenital hearing loss can be evident at birth, even if some cases may not be revealed until the first years of life, because of a late-onset [7, 8, 9, 11].

To date, more than 400 syndromes associated to hearing disorders have been identified. The most frequent are: Usher syndrome (a progressive SNHL associated to retinitis pigmentosa), Waardenburg syndrome (moderate-profound SNHL associated to dystopia cantorum and a typical dyschromia of skin, hair and eyes), Pendred syndrome (frequently pre-lingual progressive SNHL associated occasionally to goiter and to enlarged vestibular aqueduct and cochlear dysplasia). Also some craniofacial malformative syndromes (i.e., Goldenhar syndrome, Franceschetti syndrome, Apert syndrome) can lead to conductive or mixed hearing loss.

Prenatal forms of hearing loss can also be related to gestational infections, such as toxoplasma, rubella, herpes, HIV. Among infectious diseases, cytomegalovirus infection is most frequently responsible of neonatal SNHL and can also be responsible of delayed onset of SNHL (25% of hearing loss in children before 4 years of age) [7].

Ototoxicity (i.e., chemotherapics, aminoglycosides) can also be responsible of prenatal hearing loss, as well as maternal metabolic diseases (i.e diabetes mellitus, renal or liver failure) or alcoholic/drug abuse [12].

Perinatal cases include hypoxia occurred during a difficult labour and jaundice [7, 12, 13].

Acquired postnatal forms of hearing loss can be due to meningitis, viral infections (i.e., mumps, measles, cytomegalovirus), noise exposure or cranial traumas [12, 14].

Finally, conductive hearing loss (CHL) represents another chapter of hearing disorders in children. The most common form of transitory acquired CHL is recurring or persistent otitis media, responsible of about 75% of cases [15]. Less frequently, congenital middle ear anomalies (such as ossicular malformations or oval window absence) or congenital cholesteatoma can lead to a persistent CHL [16].

DIAGNOSIS

Universal Neonatal Hearing Screening

The UNHS is a crucial instrument for the early detection of hearing impairment. It consists of TEOAEs testing in all newborns, followed by automated ABR (AABR), when the registration of otoacoustic emissions fails or when there are risk factors for hearing loss. These measurements are performed through noninvasive techniques and allow to identify the physiological cochlear activity nor moderate-severe degrees of hearing loss. UNHS should be performed within 1 month of life [3, 4].

Children who do not pass TEOAEs nor the AABR, should be referred to an audiologist for a proper audiological assessment; children who pass UNHS but have at least one risk factor for hearing loss, should be referred to an audiologist, too, for periodic hearing assessment until the age of 3 years in order to evaluate with certainty a stable normal hearing threshold and auditory and language milestones [4].

Nonetheless, hearing loss of delayed onset, nor progressive hearing loss, cannot be identified by UNHS. For this reason, it has been recommended to evaluate with particular attention also all children with risk factors for hearing loss, establishing a tight audiological follow-up within the first years of life. It is imperative to recognize these cases as early as possible, in order to ensure the best possibilities to correct the hearing function properly [4].

Audiological Evaluation

An accurate history taking (particularly focusing on familiar hearing loss, risk factors, comorbidities) and the otoscopic inspection are the first steps in the assessment of hearing impairment in children.

The Joint Committee on Infant Hearing [4] states that children who fail screening and re-screening, should be evaluated by an audiologist in order to perform an air or, when indicated, bone-conducted ABR in order to assess the hearing threshold level. In fact, during infancy, electrophysiological techniques are considered the gold standard for auditory threshold measurement: ABR in order to assess hearing level at high frequencies, ASSR (auditory steady state response) at low-mid frequencies [3, 17]. Tympanometry should always be performed in order to evaluate the tympanic membrane and middle ear impedance, and also the acoustic reflex threshold should be determined [3].

In the early childhood, the audiological evaluation must be individualized and set depending on the age and the level of collaboration of the little patient. Starting from 6-8 months of age, other audiological tests can be performed such as behavioral audiometry, visual reinforcement or conditioned-play audiometry. Peep-show can be used from the age of 3-4 years. Conventional and vocal audiometry can be performed with a sufficient degree of reliability starting from the 5th-6th year [4].

During the audiological evaluation of children, it is also important to assess the perceptive abilities and speech and linguistic milestones. Also with the help of a speech therapist, it is necessary to evaluate the language acquisition, nor the transition from the prelinguistic to linguistic communication as well as the vocabulary expansion, especially in children with hearing aids in order to ensure the best speech and language development [3, 4, 18].

Infectious Disease Assessment

A difficult diagnostic challenge is represented by congenital infections, related to gestational or perinatal transmission. In particular, cytomegalovirus (CMV) infection is one of the most frequent causes of neonatal SNHL, and it is responsible for about 25% of hearing loss (mono or bilateral) within the first 4 years of life [7, 19]. Considering the heterogeneity of CMV infection, a careful audiological follow-up is recommended. In case of suspected CMV infection, a PCR blood search of CMV DNA on Guthrie card nor a urine search of CMV DNA, has been recommended within the first two weeks of life, in order to discriminate a prenatal from a perinatal/postnatal infection [20, 21, 22]. The diagnosis of congenital CMV is to be determined no later than the 1st month of life, in order to provide the adequate treatment [23]. Although a CMV vaccine is yet under study in order to reduce the maternal infection during pregnancy, the recommended treatment for infected symptomatic children is represented by antiviral therapy (6 weeks intravenous ganciclovir or 6 months oral valganciclovir); recent data in literature show a reduction of hearing and neurodevelopmental sequelae after this treatment [22, 24].

The onset of postnatal acquired infectious disease (such as *Haemophilus influenza* type b, mumps, measles, rubella), and therefore of related hearing loss, has been reduced due to the introduction of conjugate vaccines.

Neuroimaging

Imaging procedures are essential in order to identify possible structural abnormalities of the temporal bone and, in particular, malformations of the middle and/or inner ear [25]. Pendred syndrome is a typical example in which neuroimaging has a prevalent role in the diagnostic work-up. This autosomal recessive syndrome, responsible of about 7.5% of hearing loss in children [26], is caused by a SLC26A4 mutation (encoding for pendrin protein, a transmembrane anion transporter) [27]. It is characterized by congenital or short onset and typically fluctuating and progressive SNHL, more frequently of the high frequencies and often with a conductive quota associated, and sometimes by thyroid pathologies [28]. A pathognomonic element of this syndrome, although not exclusive, present in about 80% of cases, is the enlargement of the vestibular aqueduct (EVA), sometimes associated to a Mondini cochlear dysplasia [29].

Radiologic assessment, in particular temporal bone CT, is particular necessary in case of cranial trauma; it has been reported that a temporal bone fracture could represent a potential cause of conductive, sensorineural or mixed hearing loss in about 23-64% of cases [14, 30].

Also, CT scans are essential in view of surgical interventions, for example before a cochlear implant or a cholesteatoma surgery [31, 32]. During the last decade, also Cone Beam CT (CBCT) has been proposed to study the temporal bone and the middle ear [33].

Neuroimaging is indispensable in all children with CHL associated to a normal otoscopy and in absence of other risk factors: only a radiologic assessment could highlight, for example, congenital minor ossicular malformations [16].

A magnetic resonance imaging (MRI) of brain, central auditory system, brainstem and pontocerebellar angle and inner ear is also recommended in all children with permanent hearing loss. It can allow a detailed study of the 8th nerve and the inner ear, particularly of the membranous cochlea, the vestibular system and semicircular canals [34]. MRI is important especially for those children showing auditory neuropathy or dyssynchrony [35].

Genetic Assessment

There are numerous types of genetic based hearing loss, syndromic or not. More than 400 syndromes associated to hearing disorders have been described so far; nonetheless genetic forms of hearing loss can be monogenic diseases, caused by little mutations in specific genes. In the last 30 years, there has been a rapid advancement of genetics and of DNA analysis techniques. Therefore considering the clinical features of little patients, the geneticists should choose the most suitable genetic tests case by case. For this reason, the collaboration between the audiologist and the geneticist is extremely important when approaching the diagnosis of hearing loss in children [7, 9].

Mutations of GJB2 (gap junction beta-2) gene, encoding for connexin 26, is responsible for more than 50% of non-syndromic autosomal recessive SNHL in children and about for 40% of sporadic cases [2, 11]. The investigation for these mutations and also for those on GJB6 (encoding for connexin 30) has become an essential part of the diagnostic work-up of hearing loss in children [8, 9, 36]. Frequently, these genetic forms are associated to severe or profound hearing loss, but the same mutation can lead to a large range of phenotypes and,

therefore, to a various hearing thresholds (from mild to profound) [37, 38]. Moreover, hearing loss can be progressive and not necessarily present at birth [39].

When hearing loss is syndromic, an accurate physical exam is important in order to recognize pathognomonic characteristics that could suggest a specific diagnosis. A comprehensive head and neck inspection is recommended and, in particular, the attention should be focused on possible craniofacial dysmorphic features (i.e., external ear, neck and fingers abnormalities, irises, hair or skin chromatic alterations, anomalous eyes distance) [4, 40].

A kidney ultrasound and function tests are always recommended in the hearing loss evaluation in children and, in particular, when BOR (brachio-oto-renal) syndrome, HDR syndrome (hypoparathyroidism, sensorineural deafness and renal disease) or Alport syndrome are suspected [40].

Other Specific Evaluations

An ophthalmologic evaluation to assess the visual abilities eventually with funduscopy examination and an electroretinogram, should be performed, in particular to exclude possible retinopathies, as many syndromes with hearing loss are associated to ophthalmologic diseases and vision problems [40].

Also, laboratory analysis (in order to evaluate ovarian function and metabolic function), serological tests, as well as electrocardiogram, kidney and thyroid ultrasound and function tests should be performed as integral part of the diagnostic work-up of hearing loss in children [40, 41]: these could give important information in order to exclude viral infections, metabolic disorders or other syndromes associated to hearing dysfunction.

CONCLUSION

A stepwise approach to the diagnosis of hearing loss in children involves not just the audiologist and otolaryngologists, but also several other figures such as, pediatricians, geneticists, ophthalmologists, maxillofacial surgeons, neurologists, radiologists, parents, teachers. In order to improve the early diagnosis of hearing loss in children it is necessary (i) not only to implement UNHS programs [42], (ii) but also to promote the early identification of late onset and progressive hearing loss forms, even if mild, which UNHS does not recognize. Thus, an attentive and continuous surveillance of children with peculiar risk factors for hearing loss has been recommended [3, 4]: little patients with unilateral or mild hearing loss deserve a careful attention, as well as children with bilateral profound SNHL. In fact, if not properly identified and treated, also those children with mild-moderate hearing loss show the same risks in language developing as well as in lowering their social and scholastic performances [43].

It is mandatory to assure always the earliest possible intervention when facing hearing loss in childhood; hearing rehabilitation and, when necessary, speech therapy intervention should be set as soon as possible in order to allow the develop of adequate speech, language, cognitive and behavioral abilities [4].

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Chapter 44

HEARING LOSS AFTER TRAUMATIC CONDITIONS: HISTOPATHOLOGY AND CLINICAL FEATURES

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ABSTRACT

The human ear is the most susceptible organ to damage from the changes in pressure caused by a blast wave. The sensory hair cells are the primary target of noise trauma. Many are the symptoms that patients exposed to blasts have developed such as dizziness, clumsiness, imbalance and vertigo and have been associated with traumatic brain injury.

The auditory impairment is also reported in association to the blast injury. The peripheral auditory dysfunction is associated with traumatic brain injury due to the blast exposure and also increases the vulnerability of the central auditory pathways in the central nervous system to blast-induced injury. Previous studies have shown that deafness is observed when the loss of outer and inner hair cells, physical rupturing of cochlear structural membranes, and swelling and degeneration of the spiral ganglion neurons.

Many activities involving changes in atmospheric pressure are becoming common: airplane traveling, scuba diving, or hunting are some of these activities. However, other professional activities may also play an important role on the pathogenesis of this kind of situation, as a military duty, professional scuba diving, and many others. The traumatic brain injury that can be followed after these situations is a neural damage in the brain following a closed-head or open-head injury. Many studies have shown the risk of ear trauma on this situations, however only few people are aware of prevention measures.

Thus, our objective is to review the concepts of traumatic injuries of the ear, focusing on the epidemiology, diagnosis, and to highlight the mechanisms leading to both sensorineural and conductive hearing loss secondary to these circumstances.

INTRODUCTION

Hearing loss is the most frequent sensorial impairment in the world, specially in low and middle income countries. Almost 5% of the world population (360 million people) is affected by hearing loss [1, 2]. Hearing deficits are highly prevalent among older adults and are associated with declines in cognitive, physical, and mental health, especially in the geriatric population [3, 4].

Trauma situations, such as barotrauma and head trauma, can lead to temporary or permanent conductive or sensorineural hearing loss, which can lead to quality of life impairment. Hearing loss is a common functional disorder after trauma, and may be caused by ossicular, labyrinthine or brain lesions. In minor head trauma, a study demonstrated that 15% of the patients complained of vertigo, 10% complained of hearing loss, and 2% complained of tinnitus [5]. In the USA, it is estimated that 200 in every 100,000 children suffer head injury, and hearing loss is reported in about 23–64% of these cases [6].

Head trauma may cause hearing loss, facial palsy or dizziness. Conductive hearing loss (Figure 1) results from a defect in the conduction of sound, which may occur as a result of tympanic perforation, hemotympanum, or ossicular (ie, malleus, incus, stapes) disruption. Sensorineural hearing loss (Figure 2) may be secondary to damage of the inner ear (acute cochlear concussion, perilymphatic fistula). Dizzinnes may be secondary to trauma to the brainstem-eighth nerve complex, the semicircular canals (labyrinthine concussion), benign paroxysmal positional vertigo, Meniere's syndrome with only vestibular symptoms, perilymphatic fistula, and cervical vertigo [7].

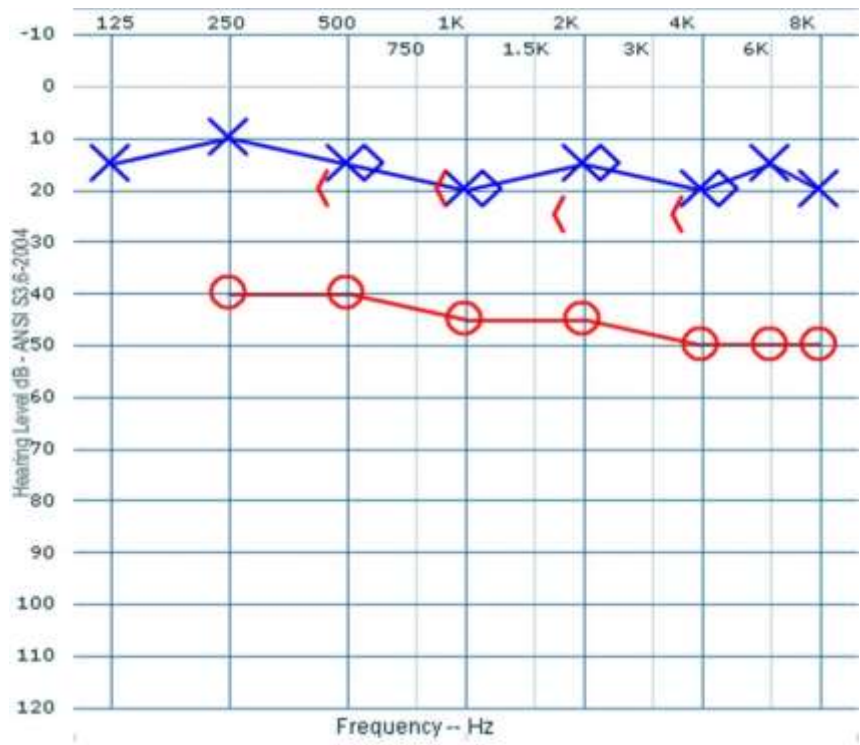


Figure 1. Pure-tone audiometry. Conductive hearing loss in the right ear.

THE EUSTACHIAN TUBE

The Eustachian tube is an osseocartilaginous canal that connects the tympanic cavity (middle ear) with the nasopharynx. It is supported in its first two-thirds by a cartilaginous portion (anteromedially located) and the last third by a bone portion (posterolaterally located). The development of the Eustachian tube is completed with 18 years of age, with significant differences between adults and children. The Eustachian tube in children is shorter and horizontalized, with 18 mm in length and angle of 10 degrees. In adults, the Eustachian tube has a length between 31 and 38 mm, with 45 degrees angle with the horizontal plane [10].

Hearing impairment is clearly associated with lower quality of life in individuals and their families and high economic impact to the society [8, 9].

The Eustachian tube is responsible for three functions: ventilation, drainage of secretions, and middle ear protection. Ventilation and consequent equalization of environmental air and tympanic cavity pressures is possible by intermittent tubal opening [11]. This occurs through the soft palate tensor muscle contraction during yawning, swallowing, or Politzer maneuver. This allows the proper functioning of the eardrum-ossicular system. The tube closes passively, due to the elasticity of fibrocartilage system, hydrostatic pressure and venous intraluminal mucus layer, providing middle ear protection [10].

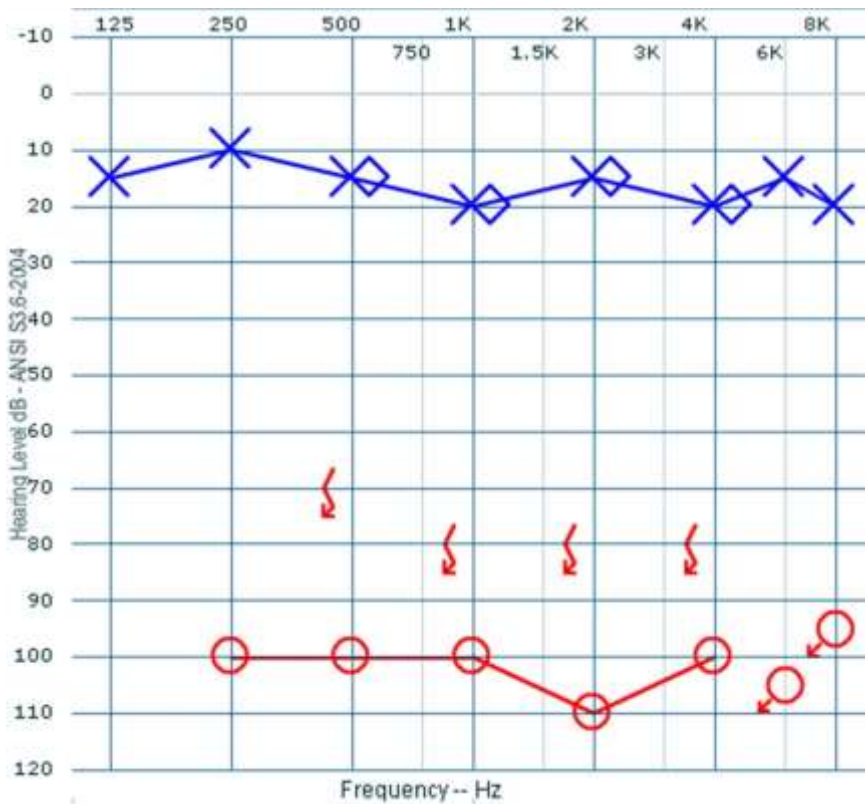


Figure 2. Pure-tone audiometry. Sensorineural hearing loss in the right ear.

Under nonphysiologic pressure changes, such as diving, ascent or descent in airplane and hyperbaric oxygen treatment, the function of the Eustachian tube can be compromised. In these situations barotrauma may occur, with resulting hearing loss due to middle ear effusion, hemotympanum, tympanic membrane rupture or perilymphatic fistula.

BAROTRAUMA

Barotrauma refers to tissue injury due to a pressure difference between an anatomical cavity filled with gas and the surrounding environment [12]. Boyle's law relates to all forms of barotrauma. The rule states that the volume of a gas varies inversely with pressure if temperature is held constant. When it affects the ear tissues and cells can cause otalgia, hearing loss, tinnitus and dizziness.

Hyperbaric oxygen treatment, scuba diving and air travel can lead to middle or inner ear injuries. These situations involve fast or extreme pressure changes and require an active and efficient mechanism for pressure equalization, often ineffective. The difference occurs due to failure of the Eustachian tube equalizing the middle ear pressure and the environmental pressure.

Ear injuries due to barotrauma can occur in up to 20% of adult and 55% of child passengers in a single flight [12] and up to 91% of patients undergoing hyperbaric oxygen treatment [13]. Barotrauma can occur to middle and inner ear, simultaneously or separately. Additionally, inner ear barotrauma is seen less frequently but is potentially more serious, and can be permanent and disabling.

Middle Ear Barotrauma

This condition is by far the most common barotraumatic otologic injury and occurs on descent (diving or flight) when the Eustachian tube does not allow air to enter the middle ear. In these cases, negative pressure in the middle ear can lead to an ex-vacuum mechanism and transudate. High pressure differences may rupture blood vessels, leading to hemorrhagic effusion and hemotympanum. In contrast, expanding air in the middle ear during ascent passively opens the Eustachian tube.

When damage is confined in the middle ear, the symptoms such as otalgia, fullness and hearing loss, usually has spontaneous remission with no sequelae in weeks. Clinical signs include tympanic membrane congestion and hemorrhage, hemorrhage or effusion in the middle ear. Audiometry may exhibit conductive hearing loss. The postmortem histopathologic findings can show rupture of the tympanic membrane, and blood in the middle ear space (Figure 3). Treatment of the middle ear barotrauma is generally symptomatic.

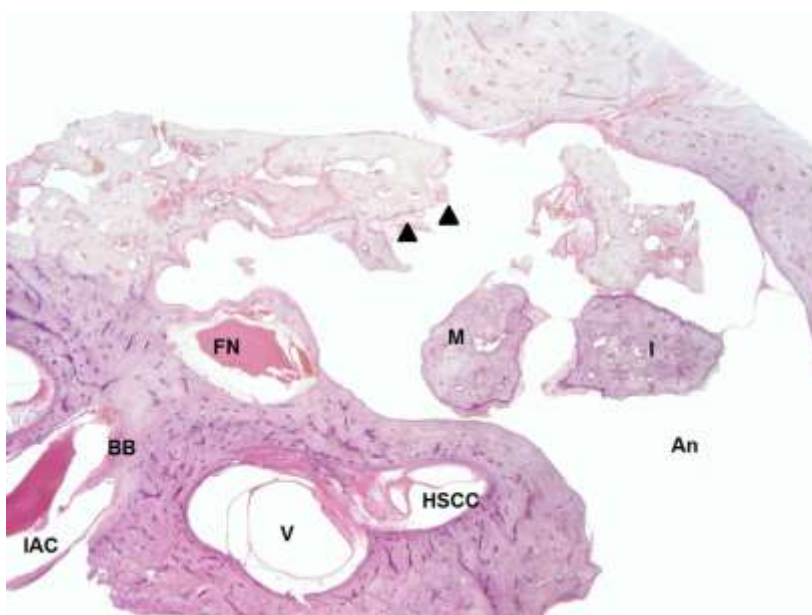


Figure 3. Example of an incudomaleolar dislocation after head trauma. Observe pieces of the tympanic bone within the epitympanic space, while there is a gap between the malleus and incus, and the origin of the fragments (arrow heads; H&E, 1x magnification). An = antrum; BB = Bill's bar; FN = facial nerve; HSCC = horizontal semicircular canal; I = incus; IAC = internal acoustic canal; M = malleus; V = vestibule.

Inner Ear Barotrauma

Inner ear barotrauma is a less common but potentially more serious situation. When damage affects inner ear, hearing loss, dizziness and tinnitus can be experienced, in different levels. Becker and Parell [14] hypothesized that three mechanisms are involved of injury to the inner ear structures: hemorrhage, labyrinthine membrane tear, and perilymph fistula through the round or oval window. Injury is produced by transmission of pressure changes within the middle ear to the cochlea by the round and oval window. Then, inner ear barotrauma results from injudicious equalization of middle ear pressure [14].

Parell et al. [15] studied 20 patients who suffered inner ear barotrauma. As initial symptoms most of the patients complained of vertigo, tinnitus, a sense of fullness, nausea and dizziness, and sensorineural hearing loss also found ranged from mild to profound in all cases, however with partial to complete recovery for all cases. Otoscopic evaluation may reveal middle ear barotrauma and confuse the physician. To differentiate between middle ear barotrauma to inner ear barotrauma, serial audiometry studies of bone and air are mandatory for those patients.

Treatment of inner ear barotrauma consists of bed rest (7 to 10 days), noseblowing is proscribed, sneezing is done through an open mouth, and avoiding strenuous activity for 6 weeks. To minimize a Valsalva effect during bowel movements, the use of a laxative is recommended. Oral steroids are also helpful, starting with prednisone therapy at a dosage of 60 mg/day and tapering this therapy to zero within 2 weeks [14]. In patients who have either

continued deterioration of hearing or newly acquired vertigo, the diagnosis of perilymph fistula must be considered and a middle ear exploration is advised.

HEAD TRAUMA AND TEMPORAL BONE FRACTURE

Head trauma is a common injury in motor vehicle accidents and can cause skull fracture. Of all the patients with skull fractures, 14-22% have temporal bone fracture associated [16]. The most common causes of temporal bone fractures include traffic accidents (45%), falls (31%), and assaults (11%) [17], predominantly in males (76.6%) [18].

Clinical presentation includes conductive hearing loss (65.8%), bloody otorrhea (61.2%) (Figure 4), hemotympanum (58.5%), tympanic membrane perforation (25.6%), facial nerve palsy (12.3%), cerebrospinal fluid otorrhea (8.5%), and sensorineural hearing loss (5.4%) [18].

Temporal bone fractures can be classified as longitudinal (Figure 5A), when the main component is parallel to the long axis of the petrous pyramid, or transverse (Figure 5B), when it is perpendicular to the long axis [19], but we can also observe them at the same time (Figure 5C). Longitudinal fracture is the most common (80%) as a result of temporoparietal trauma, while transverse fractures are mainly caused by occipital or frontal trauma.

Temporal bone fracture, especially longitudinal type [19], can lead to conductive hearing loss. It can be caused by tympanic membrane perforation, hemotympanum and interruption of the ossicular chain. The majority of patients with conductive hearing loss recover spontaneously [16].



Figure 4. Histological section of a right ear after head trauma (car accident). Observe the fracture lines within the middle ear space (arrowheads) and the presence of hemorrhage in the middle ear space (H&E, 1x magnification). GG = genniculate ganglion; H = hemorrhage; I = incus; M = malleus; ME = middle ear; SSCC = superior semicircular canal; TTM = tensor tympani muscle.

A perforation in the tympanic membrane reduces its vibration. The hearing impairment caused depends on the size of the tympanic membrane perforation, its location and the size of the middle ear cavity. When the perforation is placed in the posterior or superior portion of the tympanic membrane, the largest effect occurs. A large perforation in the tympanic membrane in humans commonly results in a 40–50 dB hearing loss [20].

After temporal bone trauma blood often fills the middle ear cavity. The sound transferred to the fluid exerts almost the same pressure on round and oval windows and affects sound conduction. Audiometry shows an average hearing loss of approximately 30 dB with nearly normal bone conduction thresholds (air-bone gap). Tympanometry can be flat because the acoustic impedance of the ear does not change despite the change in air pressure in the external auditory canal. Furthermore, the response of the acoustic middle ear reflex cannot be measured [20].

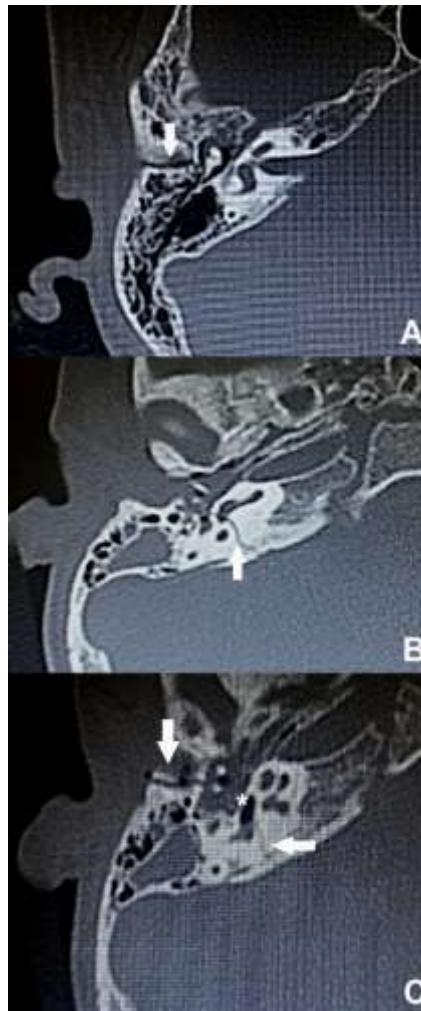


Figure 5. Axial computed tomography of the right ear of different patients. A = longitudinal fracture. B = Transverse fracture. C = Longitudinal (vertical arrow), and transverse fracture (horizontal arrow) with pneumolabyrinth (asterisk).

When interruption of the ossicular chain occurs, conductive hearing loss may exceed 60 dB if the tympanic membrane is intact. The bony conduction threshold is normal, tympanometry shows a larger than normal compliance and the acoustic reflex response cannot be recorded. The hearing threshold can be re-established by ossicular chain reconstruction surgery. The ideal prosthesis for reconstructing the ossicular chain is one that is biocompatible, easy to place, and stable over the long term with good sound transmission qualities [19].

High-resolution CT studies may be helpful for detecting such injuries. Different types of dislocations of the ossicular chain can occur: incudomalleolar joint separation, incudostapedial joint separation, dislocation of the incus, dislocation of the malleoincudal complex, and stapediovestibular dislocation. The most common types are incudostapedial and incudomalleolar joint separations [16].

Fractures that cause otic capsule violation are more likely to develop sensorineural hearing loss. Causes of sensorineural hearing loss include labyrinth concussion, fracture of the labyrinth, perilymphatic fistula and brainstem injury [16].

CONCLUSION

In summary, this chapter was focused on the epidemiology of hearing loss and traumatic injuries to the ear, and on the mechanisms related to these injuries to middle and inner ear structures as well. Early identification of a traumatic injury to the ear may lead to an adequate treatment and rehabilitation.

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Chapter 45

IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS AND CARDIOVASCULAR RISK FACTORS

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ABSTRACT

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is an acute inner ear disorder that mostly occurs unilaterally. The ISSNHL includes very different potential aetiologies, such as autoimmune and metabolic disorders, inner ear viral infections and/or impairment of the cochlear micro- circulation; among these, an impaired cochlear perfusion is one of the most widely reported hypothesis. In fact, the cochlea is provided with a terminal capillary bed and is not supplied by collateral vessels which could eventually restore blood flow in case of ischemia. Moreover cochlear hair cells have a high metabolic activity, and therefore the cochlea is particularly vulnerable to hypoxic or ischaemic damage.

There is some evidence in the current literature showing that risk factors for ischaemic vascular disease, such as diabetes mellitus, cigarette smoking, hypertension and hyperlipidaemia, can also be considered risk factors for the development of ISSNHL. Furthermore, once the cochlear damage has occurred, oxidative stress, characterized by an increase in reactive oxygen species (ROS) and consequent damages to intracellular biochemical processes, represents an important factor in the pathophysiology of ISSNHL.

Aim of this chapter is to evaluate the influence of cardiovascular risk factors among the onset of ISSNHL, and also the mechanisms of the inner ear damage, considering the evidences available in the literature so far.

INTRODUCTION

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is a relatively common disorder that can severely impact on a patient's quality of life. The aetiopathogenetic mechanism of

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ISSNHL, however it has been associated with viral, autoimmune, toxic, and vascular conditions. In particular, a microvascular impairment of the inner ear microcirculation is reported to be one of the possible causes of ISSNHL (Ciorba et al. 2013). The cochlea is provided with terminal capillaries and is not supplied by collateral vessels which could restore blood flow, if an ischemia occurs. Moreover, since cochlear hair cells have a high metabolic activity, they are particularly vulnerable to hypoxic or ischemic damage (Ciorba et al. 2013). Consequently, some Authors have identified that risk factors for ischaemic vascular disease could also be involved in the pathogenesis of ISSNHL (Ciorba et al. 2012).

ISSNHL has different presentations in terms of severity of sensorineural hearing loss, ranging in severity from mild to profound, including low and high pitch patterns, and can affect people of any age. It is likely that the severity of the hearing loss, at the audiogram, could reflect the severity of the ischemia nor the cochlear sector in which the ischemia has occurred.

IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS (ISSNHL) AND CARDIOVASCULAR RISK FACTORS

Some Authors have indicated that risk factors for ischaemic vascular disease, such as diabetes mellitus, cigarette smoking, hypertension and/or hyperlipidaemia, can also be considered risk factors for the development of Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) (Aimoni et al. 2012; Quaranta et al. 2008; Haubner et al. 2011; Lin et al. 2008; Stachler et al. 2012).

Cochlear microvascular disorders can be related either to microembolic and/or thrombotic events (Ciorba et al. 2013; Lin et al. 2008). A better understanding of the relationships between cochlear blood flow and hearing function is fundamental for improving treatment and diagnosis of deafness that potentially arises from circulatory abnormalities. However, achieving such understanding is challenging also experimentally due to the difficulties involved in monitoring cochlear blood flow. The study of cochlear microcirculation should include *in vivo* imaging of blood flow with micron-scale resolution; since the deep location of the cochlea within the temporal bone at the skull base, this is very difficult to achieve (Monfared et al. 2006; Canis et al. 2010; Ciorba et al. 2013). Consequently, most of the hypothesis available in the literature among the cochlea physiopathology arises from observational studies.

Aimoni et al. particularly evaluated the role of cardiovascular risk factors in ISSNHL, and observed that diabetes mellitus and hyperlipidaemia can be considered as possible risk factors for the onset of ISSNHL (Aimoni et al. 2013). The role of hypercholesterolemia has also been studied by Chang SL et al.; specifically, the Authors indicated that this condition may represent an independent risk for the occurrence of ISSNHL (Chang et al. 2014). Also Quaranta et al. and Haubner et al. investigated the role of the vascular hypothesis in ISSNHL mainly studying the role endothelial dysfunction, that can linked to cardiovascular risk factors, in the inner ear microcirculation. They have detected an increased expression of circulating adhesion molecules (VCAM-1) in patients affected by idiopathic sudden sensorineural hearing loss, thus confirming the role of vascular involvement in ISSNHL pathogenesis (Quaranta et al. 2008; Haubner et al. 2011). Ballesteros et al. have identified that

patients with ISSNHL had a higher prevalence of the 807T thrombophilic polymorphism of platelet glycoprotein Ia/IIa; platelet glycoprotein Ia/IIa is the major platelet collagen receptor and is responsible for platelet adhesion to the exposed vessel and it is reported to be involved in platelet-platelet aggregation in vascular diseases (Ballesteros et al. 2009; Ballesteros et al. 2012).

ISSNHL CARDIOVASCULAR RISK FACTORS AND OXIDATIVE STRESS: PHYSIOPATHOLOGY OF THE DAMAGE

Particularly, oxidative stress has been proposed to be involved in the physiopathology of the micro-vascular damage, when ISSNHL occurs. It has been reported that an increased level of intracellular reactive oxygen species (ROS) may be responsible for cochlear damage, therefore, the identification of possible cochlear ROS species and sources, could allow to develop new approaches to the prevention and rational treatment of specific inner ear disorders such as ISSNHL. In other words, the identification of the cellular mechanisms involved in the pathogenesis of the cochlear damage, at least could help us to contrast the cochlear cellular loss (Capaccio et al. 2012).

So far, identified ROS species among cochlear cells include: superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), hypochlorous acid ($HOCl$), NO, and peroxynitrite ($ONOO^-$) (Khun et al. 2011). Main sources of ROS production within the cochlea seem to be the mitochondria of inner ear hair cells and/or enzymes such as xanthine oxidase and NADPH oxidase. Once generated, the intracellular ROS are responsible for direct damage to lipids, proteins and DNA, triggering apoptosis or necrosis (Yavuz et al. 2005; Kuhn et al. 2011; Bovo et al. 2007). Also, it has been observed that the different cellular components of the cochlea, does not share the same vulnerability to injury induced by ROS. In particular, outer hair cells seem more susceptible to damage induced by free radicals especially those at the base of the cochlea, while supporting cells have a greater capacity of survival (Yavuz et al. 2005; Kuhn et al. 2011; Bovo et al. 2007). Also, glutathione (antioxidant agent) has been reported to be mainly expressed in the most apical hair cells and NOX3, responsible for the production of superoxide, to be mainly expressed among hair cells of the cochlear base nor in the spiral ganglion neurons (Yavuz et al. 2005; Kuhn et al. 2011; Bovo et al. 2007).

In addition, recent evidences suggests that, in some conditions, oxidative stress may cause further damage by triggering further endothelial dysfunction within inner ear microcirculation; this could be further responsible of further damage in case of ISSNHL, and at the same time, it could also represent a new and very interesting therapeutic target (Ciccone et al. 2012; Ciorba et al. 2012; Cho et al. 2012; Kuhn et al. 2011).

CONCLUSION

ISSNHL results from injury to the sensory components (i.e., hair cells) or neuronal components (i.e., auditory nerve cells) of the inner ear. Cardiovascular risk factors and therefore oxidative stress, characterized by an increase in reactive oxygen species (ROS) and

consequent damage to intracellular biochemical processes, represents an important factor in the pathophysiology of ISSNHL.

Targeting the oxidant response by antioxidants and by modulating specific enzymes (e.g., NO synthases, NADPH oxidase) could represent a potential therapeutic strategy; however, the therapeutic role of antioxidants in the management of hearing loss still is debated nowadays (Capaccio et al. 2012). On the other side, monitoring cardiovascular risk factors could play a role in prevent the onset of ISSNHL, at least in some cases.

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Chapter 46

HEARING LOSS OF VOLGA-URAL REGION IN RUSSIA

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ABSTRACT

We studied the molecular basis of NSHL in Volga-Ural region. The Volga-Ural region of Russia is of particular interest, because its ethnic populations mostly belong to the Turkic, Finno-Ugric, and Slavonic linguistic groups and have complex ethnogenesis and combine the Caucasian and Mongoloid components in various proportions. The data on the prevalence of hereditary non-syndromic sensorineural hearing loss in the Volga-Ural region was received. It was 5.7 per 100000 (1:17543) of the population. The heterozygous carrier frequency of c.35delG, c.167delT and c.235delC mutations of the GJB2 gene in 17 populations of Eurasia was revealed. The analysis of the spectrum and frequency of mutations in genes GJB2, GJB6, GJB3, 12S rRNA, tRNA^{Ser}(UCN), SLC26A4 and SLC26A5 in patients with non-syndromic sensorineural hearing loss from Bashkortostan Republic was performed. The mechanism of accumulation of non-

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syndromic sensorineural hearing loss caused by c.35delG mutation in Volga-Ural region is analyzed on the basis of haplotype analysis. The age of c.35delG mutation in the GJB2 gene in populations of the Volga-Ural region was defined. New approaches are developed to prevent hereditary sensorineural hearing loss and to improve medical and genetic consulting for patients with the inherited form of hearing impairment in Volga-Ural region.

Keywords: hearing loss, genes *GJB2*, *GJB6*, *GJB3*, *12SrRNA*, *tRNASer(UCN)*, *SLC26A4* and *SLC26A5*

According to various sources, congenital deafness is found in 0,05% -0,1% of the children; what is more, the majority of sick children (92%) suffer from sensorineural deafness (NSD). In most cases (about 90%) they are children of hearing parents and their families had no cases of hearing-impaired relatives. Depending on the nature of its cause, deafness is usually divided into two large groups: hereditary and acquired. Acquired hearing loss occurs due to the influence of various adverse environmental factors on a fetus, an infant or an older child. Depending on the nature of deafness, they distinguish between conductive and sensorineural types, meanwhile intermediate and mixed forms are frequently observed. Mixed hearing loss is characterized by the presence of both types of impairments: conductive and sensorineural. The cause of conductive hearing loss is a damage of the outer and middle ear and nasopharynx. Anomalies of the pinna and ear canal (atresias, microtias, development abnormalities of the auditory ossicles or otostapes fixation, etc.) can be attributed to the pathology of the external ear. If we talk about the abnormalities of the outer and middle ear, it is obvious that these types of pathologies are congenital; with age conductive type of hearing loss develops mainly due to otosclerosis (Duman et al., 2013).

Sensorineural deafness may be determined by the damage in different parts of the inner ear: the cochlea (the organ of Corti), the vestibulocochlear nerve, the pathways or the relevant structures of the brain. Sensorineural hearing loss is usually divided into cochlear (it occurs when hair cells in the organ of Corti are damaged) and retrocochlear in which cochlear neuritis is diagnosed (Tavartkiladze et al., 1996; Altman et al., 2003). A number of anomalies in the structure of the inner ear have been described in the result of pathomorphological studies of temporal bones in deaf individuals. It was found that congenital deafness may be determined by primary changes in the cochlea itself (Fishman et al., 1996).

Until 1995, clinical researchers had to face significant difficulties in the study of NSD, as before the methods of molecular genetic analysis of hereditary forms of hearing loss and deafness had been introduced into medical practice, scientific literature mainly had the descriptions of genealogy with the hypothetic types of inheritance and the attempts of segregation analysis. It was impossible to prove the hereditary nature of hearing loss in the families with sporadic cases. (Fishman et al., 1996). Assortative marriages and intermarriages between the hearing-impaired and deaf individuals should be specifically noted, as they play an important role in the spread of certain forms of deafness and hearing loss, having complex etiology, pathogenetic and epidemiologic mechanisms. Thus, molecular analysis is the only way of non-syndromic deafness adequate diagnosis, especially in the absence of genealogic pedigree data.

The most common form of hereditary deafness is the so-called nonsyndromic or isolated form, characterized by hearing loss only. In some forms of hereditary deafness there is a combination of hearing loss and abnormalities of other organs or systems. They are usually denoted as syndromic forms. In some syndromes, besides hearing impairment, there are also observed vision, thyroid, pigmentation disorders or kidney pathologies, etc. (Everett et al., 1999). One of the most world common forms of syndromic deafness, that can be found in 3-6% of all congenital deafness cases, is Usher syndrome (Nance, 2003; Duman et al., 2013). Usher syndrome, in its various forms, is a combination of hearing loss and vision impairment. Waardenburg syndrome is the cause of hearing loss in about 2 - 5% of congenital deafness cases (Ouyang et al., 2002; Morton, 2006). This syndrome is characterized by skin and hair pigmentation abnormalities combined with minor facial anomalies in addition to hearing loss. At the present moment, there are more than 400 syndromes combined with hearing loss pathology (OMIM 2013).

Clinical polymorphism of many syndromic and nonsyndromic hereditary forms of hearing loss and deafness is primarily determined by genetic heterogeneity of this pathology.

The number of patients with hearing impairments in Russian Federation exceeds 13 million people; more than 1 million of them are children. Total deafness is recorded in 1 per 1000 newborns. Moreover, during the first 2-3 years of life, 2-3 children lose hearing. 14% of people aged from 45 to 64 and 30% of people aged over 65 have hearing impairment. According to WHO, over 30% of the world population will suffer from hearing impairment in 2020 (Tavartkiladze et al. 2010).

During the targeted screening of the child population for the hearing impairment in several countries (England, Germany, Italy, Spain, Sweden, Finland, USA), averagely, deafness was detected in 1 per 650 newborns. The screening was carried out on the basis of complete audiological examination (Snoeckx et al., 2005). According to the data of various authors, it is noted that in the US at least 1 per 1000 live newborns is born with moderate or severe bilateral NSD, including 4 completely deaf children per 10,000. It is three times more than Down's syndrome, six times more than spina bifida and 50 times more than phenylketonuria (Petersen et al., 2006).

The analysis of children's age characteristics at the time of diagnosis in surdologopaedic offices of Russian regions showed that the diagnosis of hearing loss and deafness was untimely: children under 1 make only 5% of the total number of the examined; aged from 1 to 3 - 14%; about a third of children (28%) is placed in the dispensary registration list at the age of 3-7; 30% of children had hearing impairment detected at the age of 7-14 and 23% at the age of 14-18 (Tavartkiladze et al., 2010).

It is quite a difficult task - to get a complete picture about the frequency of hearing impairment among children, since numerous criteria must be taken into account: the nature of pathology, age of onset, degree of hearing loss, the child's age, family history, and character of the various complications during mother's pregnancy and labor, past illnesses, place of study, and others. Children with severe hearing loss initially fall into a specific group and they are available to account for the prevalence registration of deafness due to the possibility of studying in specialized correctional institutions. While children with mild and moderate degrees of NSD often do not get under audiologists' supervision, because they can study at an elementary school and not complain about hearing loss during medical examinations. It requires specific diagnostic and screening programs, including genetic testing, to identify such forms of children's hearing loss that mainly develop during the first year of life.

In practice, it is often quite difficult to differentiate congenital hearing loss from hearing impairment occurring postpartum during the first year of life, especially if the degree of sound perception impairment is slight and the progression of the process is slow (Cryns et al., 2004; Tavartkiladze et al., 2010).

The data on the prevalence of prelingual non-syndromic sensorineural deafness in the world literature is quite scarce. Thus according to The Gallaudet Encyclopedia of Deaf People and Deafness (1986) and The Encyclopedia of Deafness and Hearing Disorders (2004), the prevalence of congenital deafness is 50 per 100 000 in the US, 47 per 100 000 in France and 46 per 100 000 in the UK. In Europe, the incidence of congenital autosomal recessive deafness is averagely in 1 per 5000 newborns, autosomal dominant in 1 per 10000, X-linked in 1 per 100 000 boys (Alvarez et al., 2010; Duman et al., 2013). According to the register of British Columbia (Canada), the frequency of the dominant deafness is 0,19 and recessive is 0,25 per 10,000 newborns (Petersen et al., 2006; Alvarez et al., 2010).

Diagnostic screening programs for assessing the frequency of congenital hearing loss in newborns are carried out in a number of European and Asian countries, as well as in the United States (Tsukada et al., 2010; Duman et al., 2013).

In the former CIS countries in the period from 1983 to 1989, a study on the prevalence, etiology and clinical features of sensorineural hearing impairment in children of the Republic of Uzbekistan was carried out (Agzamhodzhaev SS, 1989). It was shown that NSD occurred in 9,7 per 10000 children on the territory of the Republic of Uzbekistan. The hereditary nature of the disease is established in 44% of cases. Isolated hearing impairments were detected in 94,8% of children and syndromal hearing impairments in 5,2% of cases.

Research on the epidemiology of hereditary deafness forms was carried out in a number of regions of the Russian Federation in the framework of integrated health and population-genetic survey of a region, providing a wide range of hereditary diseases detection (including different forms of hearing loss), together with the study of the genetic structure peculiarities. That made it possible to explain the basic mechanism behind the dissemination of hereditary deafness in region's districts. In these studies it was shown that spatial differences in the frequencies of hearing loss in different regions were determined by the peculiarities of the genetic structure of the populations studied, in particular, the level of genetic subdivision and the influence of genetic drift (Shokarev R.A. et al., 2002; Panakhian V.M. 2004, Markova et al., 2005; Zinchenko R.A. et al., 2007; Shokarev R.A. et al., 2005; Zinchenko et al., 2012; 2013; Bessonova et al., 2012).

Numerous studies point to a significant contribution of genetic factors in the process of sound perception impairment (Cryns et al., 2004; Smith et al., 2005; Petersen et al., 2006; Duman et al., 2013). Almost all inheritance types are observed in the inherited forms of hearing impairment, including X-linked and mitochondrial forms. Different loci of numerous nonsyndromic forms of deafness are denoted by letters DFN, taken from the English word *deafness* and they are numbered in chronological order as they had been discovered. Autosomal dominant loci are denoted as DFNA, autosomal recessive as DFNB and X-linked as DFN. The most common form of hereditary hearing loss is nonsyndromic deafness. It is characterized by clinical polymorphism and genetic heterogeneity (Petit et al., 2001; Morton, 2006; Petersen et al., 2006). This form of the disease occurs most frequently among the patients with hereditary nonsyndromic deafness (from 30 to 75% of all cases) (Denoyelle et al., 1997; Estivill et al., 1998; Antoniadis et al., 1999; Löffler et al., 2001; Morton, 2006; Petersen et al., 2006; Tekin et al., 2010). Approximately 70-77% of all non-syndromic

deafness cases occur in autosomal recessive forms, 20-25% in autosomal dominant and all other cases in X-linked and mitochondrial forms of deafness (Morton et al., 2006).

Genetic heterogeneity of hereditary sensorineural deafness forms is determined by the fact that more than 60 genes take part in the process of embryonic development of the organ of Corti (Duman et al., 2013). Most of the mutations that cause sound perception impairment are identified in the genes encoding connexins *GJB2*, *GJB6*, *GJB3*, *GJA1*, *GJB1*. Besides, the mutations that lead to hearing loss were also found in the genes of other proteins that are widely expressed in the inner ear tissues: collagen, actins, tectorines and others. Using the method of linkage analysis more than 110 loci for hereditary nonsyndromic sensorineural hearing loss and deafness were mapped. At the present time, more than 65 genes where mutations are responsible for the occurrence of human deafness were identified. It is noteworthy that the search for genes in which mutations are responsible for the development of many hereditary defects, including hereditary deafness, got intensified with the end of major international research – the project of the human genome sequencing (Human Genome Project) (<http://www.gdb.org/>) and haplotype mapping (Haplotype Mapping Project) (<http://www.hapmap.org/>). These research programs were actually catalysts for the development of more effective and rapid technologies of decryption, generating and interpreting a large array of genetic databases (<http://www.gdb.org/>).

It was found that more than 50% of congenital nonsyndromic NSD is caused by mutations in the gene *GJB2* (connexin 26 gene) (Smith et al., 2005). The contribution of this gene to the development of some nonsyndromic and syndromic forms is 4-80% (Petersen et al., 2006; Vivero et al., 2010).

Protein connexin 26 (Cx26) is involved in the formation of gap junction intercellular contacts necessary to move ions and small molecules in the tissues of the cochlea. Six connexins are joined together forming a connexon penetrating the cell membrane, which forms a channel together with the connexon of the neighboring cell.

At the present time it is observed that in some ethnic groups there is a high frequency of heterozygous carriers of the most frequent mutations the gene *GJB2*. The most common of these are deletions of: guanine at position 35 - c.35delG, cytosine at position 235 - c.235delC, thymine at position 167 - c.167delT and replacements - p.Trp24X and p.Arg143Trp. Moreover, the mutation c.35delG occurs mainly in populations of Europe, the Middle East and North America (Rabionet et al., 2000; Mustapha et al., 2001; Najmabadi et al., 2002; Tekin et al., 2003, 2010). The mutation c.235delC is major for the Mongoloid populations and occurs mainly in East Asia among the Japanese, Chinese and Koreans. It is also recorded among the Mongols and the Altaians (Yan et al., 2003; Posukh et al., 2005).

Mutation c.167delT is widespread mainly among the Ashkenazi Jewish groups, but there are some peoples of the Mediterranean, Eastern Europe and sporadically throughout Eurasia (Morell et al., 1998; Lerer et al., 2001; Gasparini et al., 2000; Bors et al., 2004). p.Trp24X mutation is most common in India and Slovakia (Mukherjee et al., 2003; Minarik et al., 2003; Ramchander et al., 2005) and p.Arg143Trp is a major mutations in Ghana (Africa) (Brobby et al., 1998; Hamelmann et al., 2001; Nagla et al., 2004).

Currently there are more than 130 different dominant and recessive mutations in the gene *GJB2* (Connexin-Deafness Homepage). Dominant effect of many connexin gene 26 mutations is mainly being associated with the mutation location in the domains of connexin 26. It was previously shown that some mutations located in specific regions of the gene *GJB2*

may affect the assembly of various classes of homologous and heterologous connexons (Bicego et al., 2006).

In order to estimate the prevalence of hereditary forms of non-syndromic sensorineural hearing loss in the Volga-Ural region, without differentiation into types, we used the materials of a complex entire health and population-genetic examination of the population in seven districts of the Republic of Bashkortostan (RB), carried out in the period from 2005 to 2008 in collaboration with Research Center of Medical Genetics (RCMG) of the Russian Academy of Medical Sciences (RAMS) (Moscow), the information on all known patients with congenital deafness, living on RB territory was obtained from the database of the National Surdologic Center where the majority of families with hereditary hearing loss is registered, the examination records in special schools of RB for hearing-impaired and deaf, documents on medical and social expertise on inspection of hearing-impaired and deaf between the years of 2000 and 2012 years. The obtained information was specified at the moment of the study through a targeted request to the central city and regional hospitals, special schools and correctional kindergartens, as well as during expedition trips in 2000 - 2012, performed together with the staff of the Republican Surdologic Center aimed at additional clinical examination of patients and their families, as well as blood sampling for DNA analysis.

In order to carry out clinical and epidemiological research, the data on each patient that has been living on the territory of the Republic of Bashkortostan during the study period from 1 January 2000 to 1 January 2011 were collected. The criterion for inclusion in the study was the diagnosis of “hereditary sensorineural hearing loss / deafness» (G11 according to ICD-10) established on the basis of clinical, laboratory and instrumental and molecular genetic research methods in accordance with current diagnostic criteria proposed by The National Institute on Deafness and Other Communication Disorders (Omaha, USA) and recommended in 2003 by European Thematic Network on Genetics Deafness GENDEAF (Mazzoli et al., 2003).

During the study the data on the patients' ethnicity was specified through interviewing and finding out the parents' nationality up to the third generation. Particular attention was paid to the establishment of the place of birth of the probands, their parents and grandparents; intermarriages revealing in the families of the examined patients. According to the initial data analysis and, based on the diagnostic criteria for NSD, nonsyndromic sensorineural hearing impairments with a burdened family history of sound perception violations were distinguished out of the total number of isolated hearing loss/deafness cases. Thus, 246 families of patients with NSD from RB were included in the study. According to the degree of hearing loss in probands, the families were distinguished as follows: I degree of hearing loss was reported in 4 families, II degree of hearing loss - in 17 families, III degree of hearing loss - in 31 family, IV degree of hearing loss - in 62 families and deafness - in 132 families.

The ethnic composition of the examined families using molecular-genetic methods was as follows: Russians - 98 families, Tatars - 58 families, Bashkirs - 37 families, Mari - 5 families, Ukrainians - 3 families, Armenians - 3 families, mixed ethnicity - 42 families. In order to analyze the frequencies and spectrum of mutations in the genes of mitochondrial DNA, the unrelated individuals from 999 families (520 healthy donors and 479 patients with impaired auditory function) from different regions of the Russian Federation were analyzed (Table. 1).

The population sample group consisted of 2 078 DNA samples obtained from healthy unrelated individuals. The ethnic composition of the studied samples was as follows: Russians (N = 92), Belarusians (N = 97), Ukrainians (N = 90), Abkhazians (N = 80), Avars (N = 60), Cherkessians (N = 80), Ingushes (N = 80), Kazakhs (N = 240), Uighurs (N = 116), Uzbeks (N = 60), Bashkirs (N = 400), Tatars (N = 96), Chuvashs (N = 100), Udmurts (N = 80), Komi-Permyaks (N = 80), Mordvins (N = 80) and Yakuts (N = 247).

Table 1. Number and ethnicity of patients and control groups to analyze the frequencies and spectrum of mutations in the genes of the mitochondrial DNA

Ethnicity	Regions								
	The Republic of Bashkortostan		Saint-Petersburg			The Sakha (Yakutia) Republic		The Altai Republic	
	Patients	Control	Patients		Control	Patients	Control	Patients	Control
			ASD	NSD					
Russians	98	50	71	46	100	10	0	10*	-
Tatars	45	50	-	-	-	-	-	-	-
Bashkirs	30	48	-	-	-	-	-	-	-
Yakuts	-	-	-	-	-	48	120	-	-
Altains	-	-	-	-	-	-	-	64*	150
Kazakhs	-	-	-	-	-	-	-	12*	-
Mestizos	22	-	-	-	-	-	-	-	-
Other nationalities	9	2	-	5	-	7	-	2	-
Total	204	150	71	51	100	65	120	88	150

* - Also included individuals of mixed ethnicity, maternally related to Russians, Altaians, Kazakhs, respectively. ASD is a group of patients with acute sensorineural; NSSND is a group of patients with non-syndromic sensorineural deafness/hearing loss.

The clinical material collected in RB was analyzed by segregation analysis, aimed at checking the conformity of the distribution of patients and healthy ones in revealed nuclear families according to a certain pattern of inheritance - autosomal dominant or autosomal recessive. The segregation analysis was performed in order to get the share of sporadic cases using the method of maximum probability, taking into account the possibility of registration in accordance with the algorithm of complex segregation analysis, developed by Morton (Lalouel et al., 1983).

Molecular genetic studies were performed using standard methods: DNA extraction; polymerase chain reaction of DNA synthesis (PCR); amplified fragment length polymorphism (AFLP), restriction fragment length polymorphism (RFLP), hybridization on (HHL) chips (Asper Biothec Ltd); single-strand conformation polymorphism (SSCP) and resequencing.

The prevalence of hereditary nonsyndromic deafness in RB ranged from 15 to 30,11 per 10⁵ people and is one of the most common hereditary diseases among the population in some areas of RB (Zinchenko et al., 2009). The results of our research indicate that NSD is distributed unevenly on the territory of RB. Its distribution in the regions of RB is shown in Fig. 1.

The NSD prevalence in RB, totally, was 5,7 per 10⁵ (1: 17,543) inhabitants. The disease was registered in 35 (out of 54) administrative districts of the Republic. Analysis of the data shows wide variation of NSD prevalence: from 0,39 to 39,67 per 100 000 people. There are no registered cases of the disease in 19 districts of the Republic: Alsheyevsky, Bakalinsky, Belokataysky, Bizhbulyaksky, Blagovarsky, Duvansky, Dyurtyulinsky, Yermekeyevsky, Zilairsky, Kaltasinsky, Kuyurgazinsky, Mechetlinsky, Miyakinsky, Nurimanovsky, Sterlibashevsky, Tatyshlinsky, Fyodorovsky, Chekmagushevsky, Sharansky. Minimum prevalence of the disease was detected in Ilishevsky, Belebeyevsky, Beloretsky, Meleuzovsky, Gafuriysky, Ishimbaysky, Krasnokamsky districts and was less than 3 per 10⁵ people. The highest rate of 39,67 per 10⁵ was registered in the Arkhangelsky region, second place was taken by Salavatsky district and the third one by Baltachevsky (38,57 and 32,39 per 100000 people, respectively). When determining the causes of the increased disease prevalence in some areas (more than 15 per 10⁵) it was found that the highest values of this indicator may be associated with territorial dislocation of the correctional schools. This fact can be explained by the special lifestyle features of the deaf and hearing-impaired individuals.

When comparing the NSD prevalence maps on the territory of RB and maps of correctional schools for the deaf / hearing-impaired, the correspondence of high NSD prevalence rates and geographic location of this or that correctional school.

These conclusions are supported by a number of European studies of hereditary forms of hearing loss. The introduction of sign language in Europe and the creation of schools for the deaf and hearing-impaired more than 300 years ago helped to break a social isolation caused by communication defect, and, thusly, helped to increase chances of deaf and hearing-impaired individuals to marry, which, in its turn, led to increase of the number of assortative marriages and birth rate increase in this population group (Tekin et al., 2007; 2010).

Mutation c.35delG (p.Gly12Valfsx1) of the *GJB2* gene is the most common for populations of Western Europe where its frequency is 20% of all hereditary isolated hearing impairments and every 33rd resident is a heterozygous carrier (Mahdieh et al., 2009).

During the first phase of research 390 patients from 204 unrelated families of RB underwent screening for c.35delG mutations in the gene connexin 26 (*GJB2*). This deletion was detected in the homozygous state in 66 patients (58 unrelated). In 67 (56 unrelated) patients c.35delG mutation was identified in the heterozygous state and in 45 (39 unrelated) patients it was in the compound heterozygous state with other mutations in the *GJB2*. Thus, mutation c.35delG was discovered in 153 unrelated families, which is 75% of all surveyed families with NSD.

Taking into account the number ratio in families in the probands of which c.35delG mutation was identified in homo-, hetero- and compound heterozygous state, we performed the evaluation of the deletions frequency in patients, which amounted to 34% in the studied samples of patients. This result is consistent with the literature data on the high prevalence of this mutation in different ethnic groups. Basically, this mutation is recorded with a high frequency among patients with hereditary deafness in Europe, North. America and Eurasia (Man et al., 2007).

The frequency of c.35delG mutation on patients' chromosomes of Russian ethnicity was 43%, among the Tatars with NSD - 27%, among the Bashkirs with NSD - 13% ($\chi^2 = 10,644$; $p < 0,05$; $df = 2$). Therefore, there are statistically significant differences between the groups of patients (Bashkirs, Tatars and Russian)s in the frequency of c.35delG mutation in the gene *GJB2*. In the group of mestizos the c.35delG frequency was 34%. The small number of representatives of other ethnic groups in the patients' samples made impossible to carry out statistical analysis and calculate the c.35delG frequency in the gene *GJB2*. These results confirm the data on prevalence of this deletion among the patients from Europe and its lower prevalence among patients with NSD from Asia (Dai et al., 2009).

The cause of hearing loss can be considered established in 66 patients from 54 unrelated families on both chromosomes of which c.35delG mutation was identified. Both differential diagnosis of hereditary disease etiology and prospective medical and genetic counseling, including the possibility of prenatal molecular genetic diagnosis, are possible in these families. Taking into account high frequency of assortative marriages between deaf individuals (45% of RB patients), it is easy enough to explain the relative prevalence of homozygous c.35delG mutations in the gene *GJB2* (28%) among the patients with NSD.

22 mutations were identified in the result of molecular-genetic analysis of the genes *GJB2*, *GJB3*, *GJB6*, *SLC26A4*, *SLC26A5* and *MYO7A*. The spectrum and frequency of mutations found in RB patients with NSD have expressed ethnic heterogeneity. Thus, the most common mutation identified with a frequency of 42.8% on chromosomes of Russian ethnicity carriers was c.35delG deletion in the gene *GJB2*. The following mutations had frequency higher than 1%: c.314_327del14 (2,5%), c.167delT (1,5%), g.-3179G> A (1,02%) and c.224G> A (1,02%). The frequency of other mutations does not exceed 0,5%.

Following mutations were identified on chromosomes of patients with NSD, having Tatar ethnicity: c.35delG (27,8%), c.314_327del14 (6,67%), c.167delT (3,33%), g.-3179G> A (3,33%), c.235delC (2,22%), c.358_360delGAG (2,22%), c.333_334delAA (2,22%), c.310_325del14 (2,22%), c. 35dupG (1,11%); and two polymorphic variants: c.79G> A (6,67%) and c.457G> A (1,1%) in the gene *GJB2*, mutation g.919-2A> G (1 1%) in the gene *SLC26A4*. Mutations c.35delG (13,3%), c.235delC (1,67%) and r.Val27Ile (c.79G> A) + r.Glu114Gly (c.341G> A) (1,67%) and c.101T> C (3,33%) were found among the patients of Bashkir ethnicity. r.Val27Ile (c.79G> A) turned out to be the most common polymorphic variant, occurring among Bashkirs; its frequency on the chromosomes of patients with hearing loss was 15%. A small contribution of the *GJB2* gene mutations in the development of nonsyndromic deafness among Bashkirs (35%), is possibly connected to the presence of mutations in other genes involved in the process of sound perception. The following mutations were identified on chromosomes of mestizo NSD patients: c.35delG (34%), c.167delT (4,55%), c.551G> C (4,55%), c.299_300delAT (2,27%), c.314_327del14 (2,27%), c.109G> A (2,27%), c.95G> A (2,27%), c.101T> C (2,27%) and polymorphic variants c.79G> A (4,55%). c.35delG (39%) and c.299_300delAT (5,56%) mutations and polymorphic variant c.79G> A (11,1%) were revealed in NSD patients - Ukrainians, Armenians, and Mari. Thus, all the mutations and polymorphic variants detected in genes *GJB2*, *GJB3*, *GJB6*, *SLC26A4*, *SLC26A5* and *MYO7A* in patients from RB are specific mainly for NSD patients from both European and Asian populations. The most common mutation, identified in chromosomes of 34% of NSD patients from RB was c.35delG mutation which corresponds to the literature data on high frequency of this deletion among the population of Europe and the Near East (Mahdieh et al., 2009). The proportion of chromosomes with

c.314_327del14 and c.299_300delAT was 3,94%. c.314_327del14 mutation is the second most common mutation in the *GJB2* gene among the patients of RB (mainly among the patients of Tatar ethnicity). Also, c.167delT and c.235delC mutations were identified in 1% of NSD patients from RB.

mtDNA mutations affecting the auditory function are mainly found in the genes encoding components of protein synthesizing apparatus of mitochondria - rRNA and tRNA. There are mutations known (m.7445A> G, m.7472insC, m.7510T> C, m.7511T> C) in *tRNA^{Ser(UCN)}* gene causing nonsyndromic sensorineural deafness (NSD) and in 12S *rRNA* gene (m.1555A> G, m.1494C> T variations near nucleotide at position 961), leading to NSD, including after taking aminoglycoside antibiotics. Participation of these mtDNA mutations in hearing loss is confirmed by numerous studies (Berrettini et al., 2008). Violation of auditory function in carriers of m.1555A> G mutation is characterized by different age of the disease onset, varying degree of hearing loss and progression. m.1555A> G mutation was detected in samples of two family members K. (proband and her mother) of mixed ethnicity from Yakutia, as well as in two family members (proband, a son, and his mother) in Russian family from St. Petersburg. The presence of m.1555A> G mutation was verified by direct sequencing. In population samples of Vilyuysk Yakuts m.1555A> G mutation was found in population samples of Yakuts (N = 120) and it was 0,83%. m.1555A> G was not found in other samples of studied population.

Three Russian unrelated patients from St. Petersburg were found to have m.961insC insertion. Two of them, having m.961insC mutation, had IV degree of ASD from early childhood after treatment of pneumonia with antibiotics. The third m.961insC patient had a clinical diagnosis of III-IV NSD degree. m.961insC (n) mutation was detected in RB patient of Tatar ethnicity diagnosed with IV degree of NSD. m.961delTinsC (n) mutation was detected in three patients (3 Russians) of RB diagnosed with III degree of NSD. m.961T> G replacement was revealed in three unrelated Russian patients, one of them (from St. Petersburg) was diagnosed with ASD of unknown etiology, the other two (from Altai Republic) had NSD of unknown etiology that occurred at an early age. m.961T> A replacement was detected in one Russian patient (St. Petersburg) with congenital NSD, with mtDNA change, what is more, such change was detected by us for the first time. m.1095T> C mutation (the gene 12S *rRNA*) was revealed by us in two individuals, Altaians: NSD patient with IV degree and in a healthy individual from the Altai population sample. m.1005T> C mutation was found in one individual from Altai population samples, and was previously identified in a Chinese family with hearing loss caused by the use of aminoglycosides. m.827A> G mutation was detected in an individual of Russian ethnicity, from samples of patients with ASD from St. Petersburg. He had c.35delG mutation in *GJB2* gene in homozygous state. m.7444G>A and m.7445A>C mutations were found in two unrelated Russian patients with ASD and NSD (IV degree) from St. Petersburg and RB, respectively, and in three siblings from one Kazakh family (with progressive NSD (III degree) occurred in adulthood).

Nucleotide substitution m.7444G> A in conjunction with m.1555A>G mutation (gene 12S *rRNA*) with 1,33% frequency was found, for the first time, during the study of deaf patients from Mongolia (Pandya et al., 1999). The mechanism of pathogenic influence of m.7444G>A and m.7445A> C may be similar to the effects of known m.7445A> G mutation associated with hearing loss (Jin et al., 2007); it violates normal processing of precursor *tRNA^{Ser(UCN)}* and mRNA of gene *ND6*, transcribed together from the light strand.

The prevalence of the most important *GJB2* gene deletions, especially c. 35delG mutation, is well studied in a number of the world populations (Mahdieh et al., 2009; Kokotas et al., 2010c), but until recently such data on populations living in the territory of the Russian Federation have been limited (Anichkina et al. 2001; Khidiyatova et al., 2002; Posukh et al., 2005, Shokarev et al., 2005; Zinchenko et al., 2007; 2008). New data obtained in our work, allow, to some extent, to fill in the existing information gaps on the prevalence of c.35delG, s.167delT and s.235delC mutations of *GJB2* gene in the Volga-Ural region, Central Asia, North Caucasus and Yakutia.

We studied the frequency of heterozygous carrier of c.35delG among both different populations of aboriginal population of the Volga-Ural region (Bashkirs, Tatars, Chuvashes, Mordovians, Udmurts, Komi-Permyaks) and in Russians samples. In the Turkic-speaking populations of the Volga-Ural region c.35delG mutation was detected with a frequency of 1%, 0,3% and 0% in Tatars, Bashkirs and Chuvashes, respectively. Among the Finno-Ugric populations of the Volga-Ural region c.35delG mutation was detected with an extremely high frequency of 6,2% in Mordvinians, with 3,7% frequency in Udmurts and absent in Komi-Permyaks. Previously, high frequency of c.35delG (4,4%) was found among Estonians which was obvious exception among the populations of Northern Europe with low frequencies of c.35delG (Gasparini et al., 2000). Data on the frequency of c.35delG mutations among the populations of Volga-Ural region, obtained by us and in other studies (Anichkina et al., 2001; Khidiyatova et al., 2002; Shokarev et al., 2005; Zinchenko et al., 2007; Khusnutdinova et al., 2005; Dzhemileva et al., 2010), show variability in the frequency of heterozygous carrier c.35delG among indigenous populations of the Volga-Ural region.

The frequency of heterozygous carrier c.35delG detected by us in Russians (2,2%) is comparable to the data obtained in other studies of the Russian population in central regions of Russia (Anichkina et al., 2001; Shokarev et al., 2005; Zinchenko et al., 2007; Barashkov et al., 2011).

In the studied Turkic-speaking populations of Central Asia (Kazakhs, Uighurs, Uzbeks), c.35delG mutation of low frequency was found among Kazakhs (0,8%) and Uighurs (0,9%) and was not found among Uzbeks. In the Turkic-speaking populations of Siberia (Yakuts, Altaians) c.35delG mutation with a relatively low frequency (0,4%) was found among the population of Yakuts, but is not detected among the Altai population (Posukh et al., 2005).

In the studied populations of the North Caucasus (Abkhazians, Avars, Cherkessians, Ingushes) c.35delG mutation was revealed only among Abkhazians (3,8%) and Cherkessians (1,3%).

The spatial frequency distribution of c.35delG mutation in Eurasia created on the basis of the data obtained in this study and available in 2010 literature data is presented in Fig. 1. The obtained data on c.35delG mutation prevalence among different populations located on spacious areas of Eurasia, will allow, to some extent, to clarify or perhaps reconsider modern concepts of origin center, age and prevalence mechanisms of c.35delG mutation.

Thus, the data obtained by us confirm the descent gradient of heterozygous carrier frequency of c.35delG mutations from West to East: high frequency of c.35delG among the populations of Eastern Europe (Belarusians, Ukrainians), intermediate c.35delG frequency is revealed among the populations of the Volga-Ural region and Central Asia, and minimum frequency of c.35delG is among Yakuts in East Siberia.

The observed decrease gradient in c.35delG frequency generally corresponds to the data of comparative analysis of mtDNA strands in Finnish and Turkic-speaking populations of

Northern Eurasia, where reduction of Caucasoid component in the gene pool of these populations as observed, in the direction from West to East from Eastern Europe to Siberia (Khusnutdinova E. et al., 2011).

Previously, it was shown that the frequency of c.167delT heterozygous carrier in Ashkenazi Jewish population samples is averagely 4,03%, reaching 7.5% in some samples, and that there is common ancestral haplotype revealed on patients' chromosomes carrying c.167delT; that may indicate the founder effect in the origin of this mutation (Lerer et al., 2000). Prevalence of c.167delT in Eurasia is limited, mainly by the territory of the Near East, although this mutation is detected sporadically in other regions (Padma et al., 2009).

In the studied populations c.167delT mutation was found in the aboregenic ethnic groups of the Volga-Ural region: the Chuvashes (1%) and Komi-Permyaks (2,5%). These data may indicate both outspread of chromosomes having c.167delT mutation of Near-Eastern origin among the populations of Chuvashes and Komi-Permyaks and independent occurrence of this mutation as c.167delT mutation was not found among the peoples neighboring to Chuvashes and Komis.

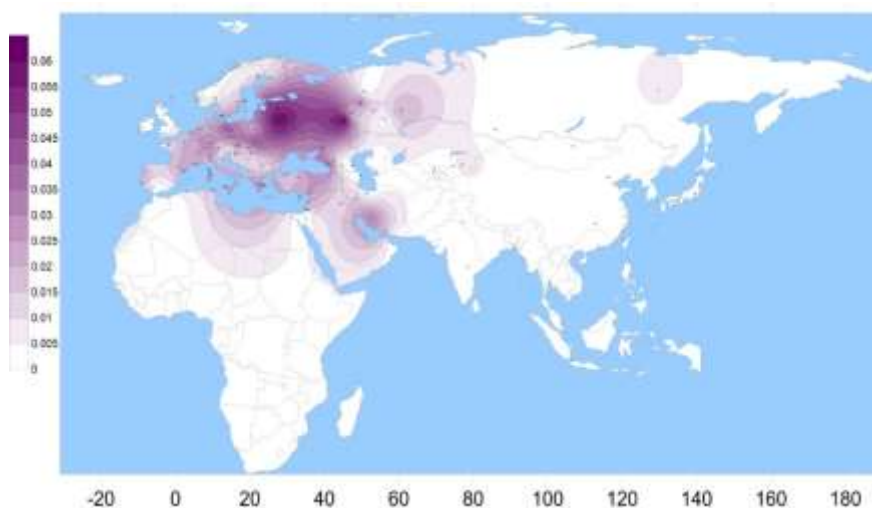


Figure 1. The spatial distribution of c.35delG mutation frequency in *GJB2* gene among the populations of Eurasia.

During the analysis of the *GJB2* gene in several Asian countries, it was found that c.235delC mutation is major in Japan, China, Korea and Mongolia; its frequency is 1,6% - 20,3% on the chromosomes in the samples of deaf patients, and the frequency of heterozygous c.235delC carrier ranges from 0,8% to 1,3% (Han et al., 2008; Dai et al., 2009), but c.235delC mutation is virtually absent among the populations of South and South-East Asia, and it is found only sporadically in other regions of Eurasia, having a complex ethnic composition of the population (Snoeckx et al., 2005).

c.235delC mutation was detected on the territory of the former Soviet Union with a frequency of 3,5% among the Turkic-speaking Altaians (South Siberia) (Posukh et al., 2005) with a frequency of 1,3% among Mordvinians (Volga-Ural region), with a frequency of 1,7% in the Avars, local group in the Caucasus with a complex ethnogenesis, and with a relatively low frequency of 0,4% in the population samples of Kazakhs.

It is interesting to note that c.235delC mutation was not detected among the Turkic-speaking Yakuts (Eastern Siberia), although, based on the data of archaeologists, anthropologists and linguists, as well as taking into account the data on mtDNA and Y-chromosome study, it is assumed that Yakuts migrated to North from their the original settlement on the Lake Baikal region under the pressure the Mongols expansion between the thirteenth and fifteenth centuries AD.

The spatial distribution of the c.235delC mutations frequency on the territory of Eurasia shows c.235delC frequency descent gradient from East to West across Eurasia and demonstrates that the Altai-Sayan region could be a potential region of the origin of this mutation (Figure 2).

Thus, results obtained by us contribute to the clarification of heterozygous carrier frequency of major recessive mutations c.35delG, c.235delC and c.167delT in the *GJB2* (*Cx26*) gene which play an important role in the development of hearing loss among the populations of Eurasia. The prevalence nature of these major deletions in the *GJB2* gene in patients belonging to different ethnic groups may further be an evidence of the alleged role of the founder effect in the origin and prevalence of these mutations in the world populations. In addition, data on the frequency of occurrence of diagnostically significant mutations in the genes *GJB2*, *GJB3*, *GJB6*, *SLC26A4*, *SLC26A5* and *MYO7A* in ethnically heterogeneous population of the Russian Federation should be considered when performing DNA diagnosis of hereditary hearing impairment.

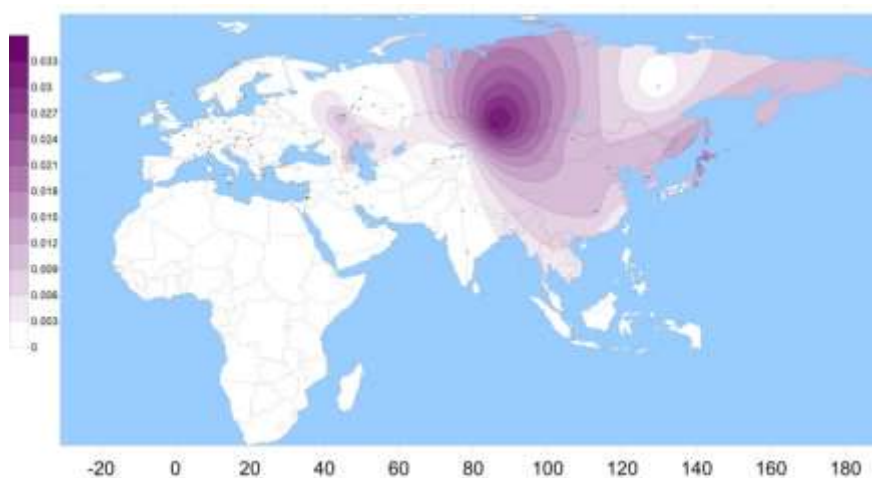


Figure 2. Spatial distribution of c.235delC mutation frequency in the *GJB2* gene among the populations of Eurasia.

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Chapter 47

SUDDEN SENSORINEURAL HEARING LOSS, AN INVISIBLE MALE: STATE OF THE ART

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Sudden sensorineural hearing loss (SSNHL), identified by Dekleyn in 1944, is an important otological disorder. It is characterized by a hearing loss greater than 30 dB over three consecutive frequencies, in less than 72 hours, with no identifiable etiology. It is a real sensorineural emergency that can become a permanent handicap if not adequately treated.

SSNHL has a prevalence of 5-20 in 100,000 inhabitants. Because of patients recovering rapidly or seeking no medical attention, the true figure might be higher. Sudden hearing loss occurs typically between 50 and 60 years of age and the lowest among 20-30. The prevalence of SSNHL is not significantly different between men and women [1, 2, 3]. There are many potential causes of SSNHL, but despite extensive evaluations, the majority of cases elude definitive diagnosis and therefore, remain idiopathic. Reports estimate that the etiology of SSNHL is diagnosed in only 10% of cases.

Therapy for SSNHL is a subject of controversy and the unknown etiology justifies heterogeneous therapeutic approaches, on one hand therapies' aim is to correct the primary risk factors (smoke, diabetes, hypertension, previous viral or bacterial infection), on the other the purpose is to act on the main etiopathogenetic hypotheses (viral infection, immunologic, vascular compromise).

Among the many treatments proposed, the glucocorticoids are the most adopted, but with different routes of administration: oral steroid, intratympanic steroid therapy and their

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combinations. Therefore, it is very important to establish an international therapeutic protocol.

ETIOLOGY

The etiology of SHL can be broken down into broad categories: viral and infectious, autoimmune, labyrinthine membrane rupture/traumatic, vascular, neurologic, and Neoplastic. There are multiple conditions within each of these categories that have been associated with sudden hearing loss. The following is a partial list of reported causes of SHL [4, 5, 6, 7]:

Infectious	Meningococcal meningitis
	Herpesvirus (simplex, zoster, varicella, cytomegalovirus
	Mumps
	Human immunodeficiency virus
	Lassa fever
	Mycoplasma
	Cryptococcal meningitis
	Toxoplasmosis
	Syphilis
	Rubeola
	Rubella
Autoimmune	Human spumaretrovirus
	Autoimmune inner ear disease (AIED)
	Ulcerative colitis
	Relapsing polychondritis
	Lupus erythematosus
	Polyarteritis nodosa
	Cogan’s syndrome
Traumatic	Wegener’s granulomatosis
	Perilymph fistula
	Inner ear decompression sickness
	Temporal bone fracture
	Inner ear concussion
	Otologic surgery (stapedectomy)
Vascular	Surgical complication of nonotologic surgery
	Vascular disease/alteration of microcirculation
	Vascular disease associated with mitochondriopathy
	Vertebrobasilar insufficiency
	Red blood cell deformability
	Sickle cell disease
	Cardiopulmonary bypass

Neurologic	Multiple sclerosis Focal pontine ischemia Migraine
Neoplastic	Acoustic neuroma Leukemia Myeloma Metastasis to internal auditory canal Meningeal carcinomatosis Contralateral deafness after acoustic neuroma surgery

CLINICAL DIAGNOSIS

The clinical diagnosis is based on:

- 1) history
- 2) audiometry
- 3) tympanometry, including stapedial reflex testing
- 4) auditory evoked potentials

1. The history, alone, allows immediate diagnosis. Details of the circumstances surrounding the SHL, the time course of its onset, the associated symptoms, such as tinnitus, vertigo or dizziness, and aural fullness should be asked. Clinical experience has shown that about 77% of patients will have associated with tinnitus and 33% vertigo [9, 10]. Moreover, patients should also be questioned about:

1. otologic surgery
2. drugs use
3. viral infections
4. systemic diseases: hypercoagulable states, diabetes and autoimmune disorders ^[11,12]

2. An audiogram (pure tone relative to the frequencies 125, 250, 500, 1000, 2000, 4000, 8000 Hz, according to the “International Organization for Standardization”: ISO) is fundamental and should be performed on all patients with SHL, in fact, the audiogram is the foundation of the diagnosis and the audiogram’s morphology provides prognostic information (Figure 1).

3. The tympanogram and stapedial reflexes directed towards a topographic diagnosis of hearing loss.

4. Tests are complete, when the hearing threshold allows, by auditory evoked potentials, because they can direct you to a pathology of the acoustic-facial package.

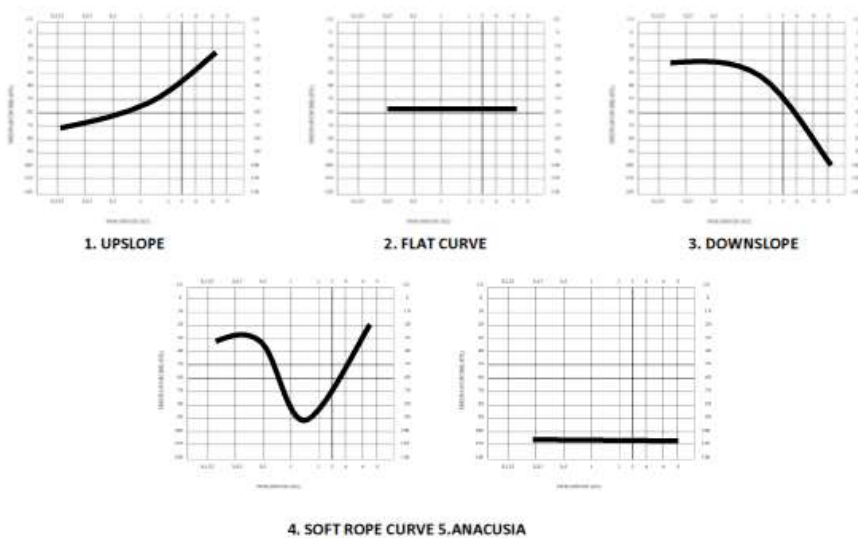


Figure 1. Most common types of curve.

PATHOPHYSIOLOGY OF THE SUDDEN HEARING LOSS

Although we can recognize only 10% of the causes of SHL, it would appear that at the base there is a hypoxic condition that causes a cell damage.

PATHOPHYSIOLOGY OF THE SUDDEN HEARING LOSS: VASCULAR THEORY

The inner ear vasculature being terminal, makes this organ at particular risk for a hypoxic and the resulting clinical picture turns out to be closely related to the physiology of the sprayed area. Must also not surprising that the circulatory system cochleo-vestibular can be affected by:

- increased blood and plasma viscosity
- sludge effect
- spasms and release of vasoactive substances
- embolism and thrombosis

PATHOPHYSIOLOGY OF THE SUDDEN HEARING LOSS: VIRAL THEORY

The first to take into serious consideration this theory was van Dishoeck in 1957^[13]. The mechanisms proposed to explain how viral infection can lead to sudden hearing loss are three (Figure 2):

1. direct invasion of the virus in the tissues of the inner ear or cochlear nerve through the bloodstream, cerebrospinal fluid, or middle ear
2. reactivation of a latent virus in the inner ear tissues: it has been hypothesized, in fact, that neurotropic virus, can infect the cochlear neurons, can remain latent and and reactivate causing a cocleite or neuritis, leading to sudden deafness
3. a systemic viral infection stimulates an antibody reaction that causes a cross-reaction with an antigen of the inner ear



A vascular deficiency in the cochlear artery determines an insult of the medium and apical part of the cochlea, therefore will only auditory symptoms with audiometric deficit at the expense of medium and low tones.



A vascular deficiency in the vestibular-cochlear artery determines an insult of the basal part of the cochlea, therefore will auditory symptoms with audiometric deficit at the expense of high tones associated at vertigo.



A vascular deficiency in the vestibular artery determines an important vertiginous symptoms vertiginous symptoms caused by damage to the three semicircular canals.

Figure 2. Occlusion cochlear, vestibular-cochlear and vestibular artery. From: <http://www.orl.uniroma2.it/ischemia.htm>.

PATHOPHYSIOLOGY OF THE SUDDEN HEARING LOSS: AUTOIMMUNE THEORY

McCabe first described autoimmune inner ear disease (AIED) in 1979 [14]. The immunological hypothesis of the sudden of hearing loss is based on the movement of cross-reacting antibodies with internal antigens or on the activation of T cells that act directly on the inner ear. A group of antigens have been proposed as targets, such as collagen type 2, β -actin, the coclina, the β -tectorina, cochlear proteins P30 and P80, the cardiolipidi, phospholipids, serotonin and ganglioside. The most documented is the CTL2 protein (choline transporter-like protein 2). Finally, in favor of an autoimmune process it has been observed a higher

frequency of allele's human leucocyte antigen (HLA) in patients who respond well to treatment with corticosteroids [15, 16, 17, 18, 19].

TREATMENT

Therapy for SSNHL is a subject of controversy and the unknown etiology justifies heterogeneous therapeutic approaches. Below is a list of treatment modalities which have been used and some of which are currently used today for the treatment of ISSNHL:

Antiinflammatory/immunologic
agents

Steroids
Prostaglandin
Cyclophosphamide
Methotrexate

Diuretics

Hydrochlorothiazide/
triamterene
Furosemide

Antiviral agents

Acyclovir
Valacyclovir

Vasodilators

Carbogen
Papaverine
Buphenine
Naftidrofuryl
Thymoxamine
Prostacyclin
Nicotinic acid
Pentoxifylline

Volume expanders/hemodilutors

Hydroxyethyl starch
Low-molecular-weight dextran

Defibrinogenators

Batroxobin

Calcium antagonists

Nifedipine

Other agents and procedures

Amidotrizoate
Acupuncture
Iron
Vitamins
Procaine

Among the many treatments proposed, the glucocorticoids are the most adopted, but with different routes of administration: oral steroid, intratympanic steroid therapy and their combinations [20].

PROGNOSIS

Clinical experience shows that the total recovery of hearing function is reported in about 25% of cases, in 50% will have a partial recovery and a 25% damage instead remains definitively [21, 22, 23]. According to a review carried out in Sicily of 270 patients can be identified the following prognostic factors:

- *TYPE OF THERAPY*: intratympanic steroids associated with systemic steroid therapy is the best treatment approach
- *TYPE OF CURVE*: the upward curve has a greater margin for improvement
- *HYPERTENSION*: patients with hypertension have a smaller chance of recovery
- *VERTIGO*: Patients with severe vertigo had significantly worse outcomes than patients with no symptoms
- *OAE*: if OAE's are present, prognosis is better [25]

CONCLUSION

Sudden sensorineural hearing loss is a chapter of great interest to the otolaryngology for the clinical relevance its possible outcomes by affecting the quality of life of relationships, both social and work of the patients affected that are isolated from the outside world. Despite various histopathological, clinical and therapeutic contributions, the etiology, the pathogenesis, diagnosis and therapy of this disease are still undefined and have contrasting aspects. The increased incidence, described by case studies reported in the literature, probably due to new and more widespread pathological noxae and the emergence of new therapeutic protocols make this topic very timely. Finally, in accordance with the literature you should always treat sudden hearing loss, because all treatments, although with different margins for improvement, give an auditory functional recovery, improving the patient's quality of life.

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Chapter 48

THE INFLUENCE OF SOUNDS IN POSTURAL CONTROL

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ABSTRACT

Postural control is a polisensory system based on the synergism of visual, proprioceptive (kinaesthetic), auditory and labyrinthic (both otolithic and canalar) inputs.

Each individual, according to age, organizes different somato-sensorial strategies in order to manage postural control. Therefore the prevalence of visual, auditory, proprioceptive and labyrinthic input management varies from subject to subject during growth.

It is known that during the first year of age, before the achievement of an erect posture, this latter is mainly managed according to auditory and labyrinthic stimuli, whereas once the bipodalic stance is achieved, afferent proprioceptive information from the foot and from the paravertebral muscles become the main stimuli for static postural control and visual input for dynamic postural control.

This shift depends on the development of anatomical and physiological systems.

Because of the anatomical contiguity of the phonoreceptor and the vestibular organs, auditory inputs can influence postural control in the form of a wave of disturbances which affects the vestibular system and general postural control. In addition, afferent auditory pathways synapse to the inferior colliculus in the mesencephalon that through the anterior tectospinal tract together to the superior colliculus, that receive visual inputs, synapse to the superior olivary complex that through the olivocerebellar tract synapses in the cerebellum, that is the organ mainly responsible for postural control. Therefore, the aim of this work will be to elucidate the role of sounds in postural control.

INTRODUCTION

Balance is a common term used by health professionals to indicate a wide variety of aspects. Such term is often used to indicate, or is associated to the words, stability and postural control. The ability of the body to balance is related to its center of mass and the area of the base of the body balancing. If the line of gravity falls in the base of the object then the object is in balance. If the line of gravity falls out of the base of the object then it will result in an imbalance and in case of a person this will fall. In order to increase the stability of an object it will be necessary to act on the base of the object or on the center of gravity. In Humans, though it is not possible to act on the center of gravity or on the base, thus human beings need to control balance through postural control, in order to allow the center of gravity to fall in its base. Human stability can be defined as the 'inherent ability' of a person to maintain, achieve or restore a state of balance, but in this case the 'inherent ability' encompasses the sensory and motor systems of the person [1]. According to a mechanistic approach a body can be stable or unstable. It is labeled stable when the structures are in equilibrium with each other and from a stationary position these return stationary after a perturbation. The human sensory motor system in order to allow the body to be defined stable must develop forces to oppose the external perturbation. This means that the human body in order to be defined stable needs to pass from an unstable state to its initial stable state, thus, human equilibrium is defined transient disequilibrium or dynamic equilibrium [2].

The anatomical and physiological components that allow postural balance are the musculoskeletal, visual, vestibular and proprioceptive systems and a continuous interaction between these systems is needed to allow proper balance [3, 4].

The vestibular system, a sensory apparatus located in the inner ear, is the main anatomical component that allows the body to maintain its postural equilibrium. The vestibular system is also essential to control the position of the head and the movement of the eyes [5].

The vestibular system is located within cavities that lie inside the temporal bone known as the labyrinth. Within the inner ear there are also the semicircular canals and the cochlea.

There are three semicircular canals: superior, horizontal and posterior, according to their position. The superior and posterior canals are both on a vertical plane whereas the horizontal canal is on a horizontal plane. Each canal has at its end an expanded area called the ampulla that opens into the vestibule. Each canal with its ampulla enters the vestibule in a different position. Each canal and its ampulla enclose a membranous semicircular duct that follows the same pattern as the canals and the ampulla in the bony labyrinth. Each semicircular canal is filled with endolymph and surrounded by perilymph.

Within the vestibules there are the utricle and the saccule, known as the otolith organs. Each sac has in its inner surface a single patch of sensory cells called macula. Each macula consists of fine hair bundles which are covered by an otolithic membrane that is jelly-like and covered by a blanket of calcium crystals. In the utricle, the macula projects from the anterior wall of the tubular sac and lies in the horizontal plane whereas in the saccule the macula is on a vertical plane, directly over the bone of the inner ear of the vestibule. Each macula consists of an epithelium of sensory cells as well as a membrane of nerve fibers and nerve endings. The sensory cells of this epithelium are called hair cells. The nerve fibers are part of the vestibule-cochlear nerve.

When the head changes position, the hair bundles are deflected by the calcium crystals and the hair cells change the rate of nervous impulse through the vestibular nerves to the brain stem.

The semicircular canals, respond to rotational movements (angular acceleration) whereas the utricle and saccule within the vestibule, respond to changes in the position of the head with respect to gravity (linear acceleration). The information these organs deliver is proprioceptive in character, dealing with events within the body. Abnormal vestibular signals cause the body to try to compensate by making adjustments in the posture of the trunk and limbs as well as making changes in eye movements to adjust sight inputs into the brain.

The other organ located within the inner ear is the cochlea, that may be defined as the sensory organ of hearing. The way this organ transmits the sound is through the cochlear nerve, a short division of the vestibule-cochlear nerve. The information this organ delivers is exteroceptive in nature, delivering sound information from an external source and converting this in action potentials.

Functionally these organs are closely related to the cerebellum and to the reflex centres of the spinal cord and brain stem that govern the movements of the eyes, neck, and limbs [6].

The vestibulos and the cochlea are anatomically in continuity, meaning that sound and balance, are closely related.

ANATOMICAL ELEMENTS OF SOUND AND POSTURAL CONTROL

To maintain a certain posture, there must be a control center that activates antigravitary muscles, this is generally provided by the somatic motor system. The somatic motor system needs to control both axial musculature and limb muscles. Because muscles never act alone but always in combination with other muscles, premotor interneurons play a crucial role in motoneuron control. Premotor interneural activation can be distinguished in medial for the axial muscle motoneurons whereas these become unilateral for the distal muscle motoneurons [7]. The reason for this difference is that proximal and axial movements, in contrast to the distal movements, are almost always bilaterally organized.

The pathways of the medial system originate in cell groups belonging to the brain stem. Part of the medial tract are the reticulospinal pathways that originate from the medial tegmental fields of the caudal pons and the vestibulospinal pathway. The vestibulospinal pathway sends fibers ipsi- and contralaterally through the spinal cord where the neck muscles premotor and motor neurons are located. This means that the vestibulospinal pathway is actively involved in controlling the head, and the neck during postural control. Other function of the vestibulospinal tract is to control the extrinsic eye movements [8]. The eyes during postural control are also controlled by the pontine reticular formation, and the superior colliculus. These two formations are responsible for head, trunk and eye movements. Interestingly the inferior colliculus, that receive, visual, somatosensory and auditory information, project to the pontine reticular formation through the tectobulbospinal tract, and to certain premotor neurons involved in horizontal head movements [9]. This is the anatomical relation between, posture, sound and visual information, that together allow a human being to control posture. Therefore, proprioception, sounds and visual input are fundamental for a proper postural control.

As afore mentioned in the previous paragraph the main organ responsible for equilibrium is the vestibule. This is innervated by the vestibular nerve, a branch of the vestibule-cochlear nerve. The vestibular part of the nerve synapses on the premotor neurons of the brain stem that then ends on a set of neurons located in the vestibular ganglia. Some projections from the vestibular ganglia reach the nuclear vestibular complex. This is functionally divided in two areas, the rostral portion that has the function to detect angular accelerations from afferents from the semicircular canals and from the head and the eyes and the ventral portion that is mainly related to postural control and muscle tone [10]. The vestibular nerve is also directly connected to the cerebellum through the inferior cerebellar peduncle [10].

The two nuclei of the vestibular complex are connected to each other and also receive ascending and descending connections. One of the most important ascending connections is that with the longitudinal medial fascicle that goes to the ventrobasal complex of the thalamus with fibers direct to the parietal ascendent gyrus that allow the vestibular inputs to be conscious. Other portions of the vestibular nerve go to the nuclei of the oculomotor, trochlear and abducent nerve, and together generate the vestibulomotor reflex, that allows compensation for head and eye movements during voluntary movements [10]. From the medial vestibular nuclei originates the medial vestibulospinal fascicle that descends bilaterally to the α e γ motoneurons of the cervical tract that allow the vestibulospinal reflex that is responsible for head stability during movements from vestibular stimuli. Lesions to the vestibulocochlear nerve may lead to dizziness, nistagmus, tinnitus or hearing loss. All these pathologies related to the vestibule-cochlear nerve lead to postural disorders or impairments [11].

SOUND AND INNER EAR

A sound is defined as a vibration produced by a vibrating object that produces pulses of vibrating air molecules. The ear can distinguish different aspects of sound such as pitch and loudness.

Pitch describes the characteristic of the sound wave that in human beings lays between a range of frequencies of 20 to 20.000 Hertz. The range of maximum sensitivity and audibility diminishes with age. Loudness is the perception of the intensity of sound, or in other words the pressure of the sound wave on the tympanic membrane [12]. The loudness is expressed in decibels and on such scale human hearing extends from 0 to 130 decibels, at such level the sound becomes painful. The head acts as a barrier between the two ears and thus a sound source at one side will produce a more intense stimulus of the ear nearest to it and incidentally the sound will also arrive there sooner, helping to provide a mechanism for sound localization based on intensity and time of arrival differences of sounds, thus helping postural control [13].

The ear canal acts as a resonating tube and actually amplifies sounds between 3000 and 4,000 Hz adding sensitivity to the ear at these frequencies. The ear is very sensitive and responds to sounds of very low intensity, to vibrations which are hardly greater than the natural random movement of molecules of air [14]. To do this the air pressure on both sides of the tympanic membrane must be equal. The outer and middle ears serve to amplify the sound signal and they do so at intensities of about 30db .

The function of the inner ear is to transduce vibration into nervous impulses. While doing so, it also produces a frequency and intensity analysis of the sound. Nerve fibers can fire at a rate of just under 200 times per second. Sound level information is conveyed to the brain by the rate of nerve firing, for example, by a group of nerves each firing at a rate at less than 200 pulses per second. They can also fire in locked phase with acoustic signals up to about 5 kHz. At frequencies below 5 kHz, groups of nerve fibers firing in lock phase with an acoustic signal convey information about frequency to the brain. Above about 5 kHz frequency information conveyed to the brain is based upon the place of stimulation on the basilar membrane. So when the sound reaches the tympanum this vibrates and such vibration causes the motion of the bones in the middle ear (malleus, incus and stirrup). The ossicles amplify the sound and send sound waves to the inner ear and into the cochlea. Once the sound reaches the inner ear this is converted in electrical impulses and these translated in the brain to sound [12].

THE INFLUENCE OF SOUND ON POSTURAL CONTROL

Because the phonoreceptors and the vestibular organ are situated anatomically close to each other, sound vibrations can influence posture control [15, 16]. The anatomical proximity of the vestibular labyrinth to the acoustic-energy delivery system, the great similarity in cochlear and vestibular hair-cell ultrastructure, the fact that both balance and auditory receptors share the membranous labyrinth, and the common arterial blood supply of the cochlea and vestibular end organs via the same end artery, all support the possibility of sound influencing postural control or causing vestibular symptoms [24]. There is also a condition known as superior semicircular canal dehiscence, a defect in the temporal bone between the apex of the superior semicircular canal and the middle cranial fossa, that induces vestibular responses to sounds [17]. These responses are known as the “Tullio phenomenon”. When exposed to sounds, patients that suffer from this condition exhibit dizziness, nausea, vomit or nistagmus. This condition may also be caused by trauma or a result of a surgical operation. Two types of mechanisms are involved in the destruction of the end organs by noise: direct mechanical destruction, and metabolic decompensation with subsequent degeneration of sensory elements [25]. A sudden sound provokes destabilization of the upright body posture, which results in greater increase in postural sway [16].

Sound loudness, frequency and sound duration in order to elicit postural responses however need to be of a certain intensity. A postural response may be considered either as an increase of the length of the stabilogram or a decrease of such length. In addition, depending on the source of the auditory stimulus the postural response may vary on a frontal or sagittal plane. To be noted, all the comparisons present in scientific literature refer to postural responses with and without sound sources, meaning that any variation is always compared to the correspondent unbiased measure. Sound sources may increase or decrease the amplitude of the oscillations of the stabilogram compared to the stabilogram obtained in silence [18].

The lengths of the sway has been shown to increase according to increases in the frequency of the sound, with higher disturbances around 4000 Hz frequencies, only in the anterior-posterior axis. Also the position of the center of pressure is influenced by sound frequency [3]. At frequencies of around 2000Hz the length of the sway and the position of the

center of pressure seem to be at a minimum variability. Sound seems to affect postural control with frequencies ranging between 1000 and 4000 Hz [15]. Higher frequency sounds are able to affect postural control. In addition postural responses are greater when a loud sound (greater than 90 dB) is applied independently from the frequency of delivery.

In humans an acoustic stimulus of 500 Hz at 90 dB applied monoaureally may also be able to lead to postural responses [22]. It doesn't seem that sounds of intensities below 90 dB are able to affect postural control. Fourier analysis of postural sway demonstrates that low frequency oscillations in the postural sway during sound-stimulus at 500 Hz are mainly under the influence of the vestibular control, whereas higher frequencies are mainly under proprioceptive control during antero-posterior sway [19].

Sound pressure level influences postural control in normal subjects [3]. The influence of sound on postural control seems to be dependent on the intensity of the stimulus. A constant tone above 95dB can produce a postural deviation towards the stimulated ear [20]. There is physiological evidence that vestibular neurons increase their firing rate in response to loud sounds [20]. An increase in the sound amplitude will initially activate irregular otolithic neurons, but few semicircular canals that will only be activated at very high intensities [20]. However, sounds of low intensities are seen to be able to evoke postural responses in blind people [21]. To be noted that normal speaking ranges are between 50 and 90 dB [22].

The duration of the sound also seems to influence to postural control [3, 23]. Increased exposure increases postural sway [3]. Sound influence seems to be critical when exposure lasts for at least 30seconds [16, 19, 24]. No responses have been seen when the sound stimulus is applied for less than 20 seconds [19].

Sound origin seems to be another factor related to postural control alterations. Moving auditory stimuli increase human body sway, in a direction dependent manner, related to the origin of the sound stimulus[18]. Monoaural loud stimulus in fact seem to affect the body sway on the lateral plane [19]. There also seems to be a relation between asymmetrical hearing loss and balance. The majority of individuals reported in scientific literature, that exhibit vestibular symptoms usually have an asymmetric hearing loss caused by trauma or exposure to very loud noises, whereas only 11% of people with symmetrical hearing loss seem to exhibit vestibular symptoms [25]. The National Health and Nutrition Examination Survey (2001–2004) database showed that for each 10 dB of hearing loss, individuals had a 1.4 times increased risk of falling [25]. However, hearing aids significantly improve balance in older adults that have progressively lost hearing during their lifespan [25]. No differences seem to be noted between male and female during postural control after sound influence with open eyes [15].

Scientific literature in regard to postural sway has showed that in groups of sighted (blindfolded) subjects and congenitally blind patients with a pair of fixed, external auditory sources located immediately adjacent (5 cm lateral) to each ear reduced the movement of the center of pressure compared to when standing in silence [25]. Meaning that during visual deprivation an auditory stimulus may help postural control.

A sound-induced saccular activation would evoke a vestibule-postural reflex, expressed as a muscular reaction in the lower limbs [19]. The sound induced reaction of the lower limb acts on the postural pattern that can indirectly act on the static posturography [26].

There are three possible explanations by which an auditory stimulus may affect postural control through vestibular activation: 1) Both auditory and vestibular receptors have hair cells classified as mechanoreceptors, so these receptors process information in a similar way; 2)

Even with a different perceptive frequency range for each receptor, if there is a very strong stimulus, this can activate a varied type of nervous cells; 3) As saccular receptors are in close proximity to the footplate of the stapes, these will likely be preferentially activated by the abrupt invar movement of the stapes [16].

In conclusion, sound may affect both positively and negatively postural control. Loud (above 90dB) and high frequency sounds (above 2000Hz) seem to negatively affect postural control, increasing body's postural sway on both an anterior-posterior axis and a medio-lateral axis. Whereas frequencies of around 2000Hz seem to both decrease the body sway and the center of pressure. Body postural sway is directly related on the sound source and on the duration of such sound stimulus with no differences between genders. There also seems to be a relation between hearing loss and balance in the elderly, that may be improved by the use of hearing aids. In addition, sound sources seem to help blind people improving their postural sway.

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Chapter 49

CHRONIC OTITIS MEDIA AND HEARING LOSS

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ABSTRACT

The otitis media (OM) is defined as an inflammatory process, infectious or not, that occurs in the middle ear cleft either as a focal or a generalized process. Because of its high prevalence and multiple clinical presentations, OM is often associated with high social cost and it can become directly and/or indirectly highly expensive. It is estimated that the annual cost of OM is more than 5 billion dollars, considering only the United States. Chronic otitis media is a worldwide problem, but is more prevalent among poor and developing countries. Otitis media can also be associated with hearing loss. Chronic otitis media with effusion is the main cause of hearing loss in children and it can progress over time to more complex conditions such as tympanic membrane perforation, tympanic membrane retraction or cholesteatoma. Hearing loss may appear at any time during the OM progress and can present with different types and degrees. As for the type, the hearing loss caused by OM may be conductive, sensorineural, or mixed. As for the degree, depending on how aggressive is the pathological process and the extension of it the hearing loss will vary from mild, moderate losses (usually conductive) to even severe degrees with severe and profound losses (usually sensorineural). The goal of the OM treatment is not only the resolution of the inflammatory process but also the improvement of the hearing deficit. This goal can be achieved simply by the reconstitution of the tympanic membrane and ossicular chain or by the use of conventional hearing aids and, more recently, by the implantation of bone anchored hearing aids. Rarely patients can present profound bilateral hearing loss as a consequence of chronic OM. In these cases, cochlear implant surgery is the best option of treatment as soon as the resolution of inflammatory process occurs.

Keywords: hearing loss, otitis media, children

1. INTRODUCTION

The otitis media (OM) is defined as an inflammatory process that occurs in the middle ear cleft. OM can be acute, generally associated to pain and fever and usually auto limited or chronic when persists for more than 3 months. According to continnun theory proposed by Paparella, the earlier forms of OM, such as acute or serous, can progress over time to more chronic forms like OM with effusion that, without mechanisms that could stop it, can progress more complex conditions like severe tympanic membrane retraction and cholesteatoma.

Because of its high prevalence and multiple clinical presentations, OM is often associated with high social cost and it can become directly and/or indirectly highly expensive. It is estimated that the annual cost of OM is more than 5 billion dollars, considering only the United States. Chronic otitis media (COM) is a worldwide problem, but is more prevalent among poor and developing crountries.

OM, in all their forms, can also be associated with hearing loss. Hearing loss may appear at any time during the OM progress, can present with different degrees and can be not associated to other symptoms. Chronic otitis media with effusion (OME), for example, is the main cause of hearing loss in children and, if is not associated to recurrent acute otitis media, the deafness will be the single children's complain.

As for the type, the hearing loss caused by OM may be conductive, sensorineural, or mixed. As for the degree, depending on how aggressive is the pathological process and the extension of it the hearing loss will vary from mild, moderate losses (usually conductive) to even severe degrees with severe and profound losses (usually sensorineural). The goal of the OM treatment of is not only the resolution of the inflammatory process but also the improvement of the hearing deficit. This goal can be achieved simply by the reconstitution of the tympanic membrane and ossicular chain or by the use of conventional hearing aids and, more recently, by the implantation of bone anchored hearing aids.

2. OTITIS MEDIA WITH EFFUSION

Otitis media with effusion (OME) can be defined as the presence of fluid in the middle ear behind an intact tympanic membrane, without symptoms or signs of acute ear infection. The fluid can appear during a viral upper respiratory infection, as a result of a poor Eustachian tube function, or as an inflammatory response following an acute otitis media (AOM). Chronic OME (COME) is defined by the documented presence of OME for more than 3 months.

The incidence of OME varies from different studies but this is a clearly very common problem. The literature supports an incidence of more than 60% of children before 2 years of age and around 90% would have at least one OME episode at school age [1, 2]. The rate is even higher in patients with developmental issues such as Down syndrome and craniofacial malformation [3].

The natural history of OME is one of resolution, with most individual episodes subsiding within several weeks. In a systematic review looking for the natural history of OM the authors found OME after untreated AOM had 59% resolution by 1 month and 74% by 3 months [4]. Other authors described a persistence of OME for 3 months or longer in about 10 to 25% of the OME cases [5]. Although, the same systematic review found that COME had only 26% resolution by 6 months.

Chronic OME can cause hearing loss, delay in language development, auditory problems and vestibular symptoms. As a result, COME can have an important impact on children's mood, communication, behaviour, learning and socialisation, affecting the patient's quality of life [4, 6, 7]. The presence of COME in early childhood was also demonstrated of having a possible impact on intelligence quotient (IQ), behaviour and reading into teenage years [6, 7]. Therefore, it is crucial to achieve the correct identification of OME as well as the hearing assessment for children with COME.

The functional impact of COME can be more intense in those children who already have a clinical condition associated with high risk of hearing loss or with development impairment. Patients with suspected or confirmed speech and language delay or disorder, autism spectrum disorder, any developmental disorder, syndromes or craniofacial disorders that include cognitive or language delays, blindness or uncorrectable visual impairment, cleft palate and any developmental delay are considered at-risk and should be evaluated in a proper manner. Children with Down syndrome, for example, have decreased motor tone of the Eustachian tube and the cleft palate, because of abnormal insertion of the levator veli palatini and tensor veli palatini muscles [3, 8-9]. The at-risk children should be evaluated for OME at the time of the condition that classified them as at-risk is diagnosed. If OME is present the hearing should be tested promptly in this population.

The recently published Updated Guideline on OME from the American Academy of Otolaryngology recommends that children with effusion for longer than 3 months (COME) should be addressed for an age-appropriate hearing test. This recommendation was based on cohort studies showing high incidence of hearing loss in children with COME, as well as on the clear preponderance of benefit over harm. There is no need for audiology evaluation for otherwise healthy children with early onset OME. However, the at-risk group of patients should be evaluated for hearing loss at any time if diagnosed with OME.

There are different tests that can be used to get a reliable response and the choice must be age appropriate. The hearing test can be done through conventional audiometry, comprehensive audiologic assessment or frequency-specific auditory evoked potentials. Most kids aged 4 years or more are collaborative enough to partake in a conventional audiometry done performed by a trained audiologist. A comprehensive audiologic evaluation is chosen for most children between 6 months and 4 years as well as for those older than 4 years that had failed at conventional study.

The impact of OME on hearing can vary from normal hearing to moderate conductive hearing loss. The average loss described is 28-dB (decibels), with around 20% of cases exceeding 35-dB of loss [10-11]. Sabo et al. performed a study comparing different audiologic techniques, age groups and middle ear condition and described that OME was associated with hearing threshold levels 10 to 15 dB higher than the normative values for the corresponding age group [12].

It is important to know that the hearing loss, as measured in decibels is a logarithmic scale of intensity, and for every 3- dB increase, there is a doubling in sound-intensity levels.

A child with normal hearing of 20 dB would experience 8-fold increase in sound intensity when compared with a child with OME and average hearing loss of 28 dB [13].

Although all periods of language development are important, a sensitive period is defined as a time interval in which an organism is biologically prepared to acquire certain behaviors as long as there is a stimulating, supporting environment. Prospective studies of children with recurrent OME suggest that mild hearing loss associated with OME in early life is associated with poorer extended high-frequency hearing sensitivity and atypical auditory brainstem pathway indices (elevated crossed, but not uncrossed, middle ear acoustic reflex thresholds, and delayed wave V auditory brainstem response (ABR) latencies) at school age but not psychoacoustic or speech-in-noise tasks. However, other studies have demonstrated compromised deficits in binaural auditory tasks such as binaural release from masking and speech-in noise listening. In some cases, difficulties resolved following treatment for middle ear disease or an extended period of normal hearing after resolution of OME [14].

The hearing loss presence and degree should be objectively assessed once the parents' perception was described as inaccurate. Brody et al. developed a 7-item self-administered survey (HL (hearing level)-7 survey) with specific questions about the perception of the hearing ability of the child. They described the survey as a reliable and internally consistent parent perception but unfortunately these perceptions had no correlation with pure tone average results for the better hearing ear [15]. Therefore, the attending physician cannot rely on parent perception to guide audiology evaluation for patients with COME. Other authors had addressed this topic finding the same result. [16].

The main goal when managing patients with COME is to resolve effusion and, consequently, restore the optimal hearing and improve the quality of life. Different treatments were described with different results.

The recent reviewed Guideline made a strong recommendation against the use of steroids (both intranasal and systemic), antibiotics, antihistamines and decongestants for COME [13]. Antihistamines and decongestants are poorly discussed in the literature, but there is a controversy about steroids and antibiotics prescription.

A recent Cochrane review looked on the use of antibiotics for OME. The authors found moderate quality evidence from 6 trials (including 484 patients) that children with OME treated with antibiotics are more likely to have complete resolution of the OME at 2 to 3 months post-randomization when compared to control group. However, there is obvious evidence indicating the higher incidence of diarrhea, vomiting and skin rash in the treated group. Analysing resolution at any time the review found low quality evidence of a beneficial effect of antibiotics and the same low quality evidence was found between the use of antibiotics and decrease in tympanostomy with tube insertion. There was poor data using hearing recovery as outcome. The authors concluded that there is evidence for both benefit and harm for the use of antibiotics and suggest that its important to have in mind the low or moderate quality of evidence described before prescribing antibiotics for such a common condition, specially because of antibiotic resistance induction [17].

A Cochrane systematic review in 2011 has found insufficient evidence for the effectiveness for oral steroids but sufficient evidence to suggest further research on this topic [18]. There is evidence from in vitro and animal models suggesting that steroids can reduce effusions and middle ear pressure but there is no clear evidence regarding the use of a short course of systemic steroids to treat OME. Based on this assumption Waldron and colleagues recently published the OSTRICH (oral steroids for the resolution of otitis media with

effusion) protocol, promising to be the first adequately powered trial to evaluate the clinical effect and the cost-effectiveness of a short course of oral steroids for OME [6].

As the natural history of OME is favourable, in most cases there is no need for a specific treatment. If the OME is asymptomatic and is likely to resolve spontaneously is possible to suggest a watchful waiting, sometimes even if OME persists for more than 3 months. The described risk factors associated with reduced likelihood of spontaneous resolution include: OME onset in summer or fall, hearing loss >30 dB HL in the better hearing ear, history of a prior set of tubes and not having a prior adenoidectomy [13]. Randomized trials suggest that healthy children could be safely observed for at least 6 months, with regular follow up at each 3 months. If there is symptoms modification, hearing loss or alterations of the tympanic membrane structure, the indication for surgery can be made. Its important to stress out that patients with OME need to be followed closely not only because of the hearing but to ensure the integrity of the tympanic membrane. OME is associated with tympanic membrane inflammation and chronic low middle ear ventilation and this environment can lead to tympanic membrane retraction. The incidence of structural damage increases with effusion duration [19].

During the watchful waiting period, autoinflation was described as a tool to help ventilating the middle ear and there are different devices available. A trial published in 2015 found modest effect when an autoinflation device was used in children with OME between 4 and 11 years [20]. However, around 80% of the affected children are under 4 years and the autoinflation is probably technically difficult to be used on this young population.

The surgical approach to COME is a tympanostomy with ventilation tube insertion. The 2013 Guideline on Tympanostomy Tubes recommends performing this procedure for children with bilateral COME (more than 3 months of OME) and hearing loss. For those patients with unilateral or bilateral COME and symptoms likely related to OME (vestibular, poor school performance, behavioural problems, ear discomfort) the guideline suggest the tympanostomy as an option. There is an option also for inserting tubes in children at-risk with OME that is unlikely to resolve quickly (with a type B tympanogram) even if its duration is less than 3 months [21].

Its treatment is broadly discussed in the literature, a recent prospective study conducted in Moldava and supported by the Mayo's Clinic compared three types of treatment of COME (adenoidectomy + tympanostomy, physical conservative treatment + adenoidectomy and physical conservative treatment alone), the T+A group normalized and had stable hearing in 95% of the ears after 12 months with less middle ear changes like adhesions, retractions and thickening of the tympanic membrane when compared to the other groups [22].

Any child with detected hearing loss secondary to OME should have a hearing test after the resolution of the OME to confirm resolution of hearing loss that was attributed to OME and to assess for an underlying SNHL.

Hu et al. in 2015, showed the impact in hearing of tube placement in patients assessed by sound field audiometry and evaluated by pure-tone audiometry: the mean sound field threshold value was 29.2 dB preoperatively and improved to 17dB, 6 to 10 weeks postoperatively in the first ones and the mean preoperative air-bone gap was 20.1 dB and this improved to 7.3 dB in the second ones.

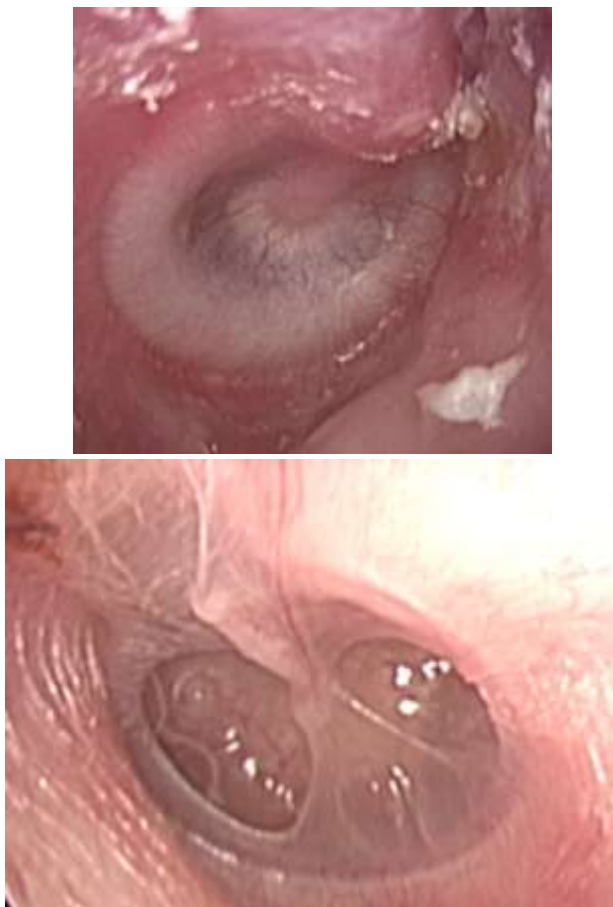


Figure 2. Illustration of an otitis media with effusion and retraction of the pars tensa. (Image of the Department of Otolaryngology-Head and Neck Surgery, Hospital de Clinicas de Porto Alegre)

Unresolved OME and associated hearing loss may lead to auditory problems, poor school performance, language delay and behavioral problems. If undiagnosed and without treatment it can contribute to the progression of OM, recurrent acute otitis media, chronic inflammation of the tympanic membrane [23-25] which can induce epithelial migration, and predispose to retraction pockets and cholesteatoma formation.

3. CHRONIC OTITIS MEDIA

Chronic otitis media COM has been traditionally characterized as an inflammatory condition of the middle ear associated with tympanic membrane (TM) perforation and otorrhea. Histopathologically, COM has been defined as a condition of the middle ear associated with irreversible inflammatory pathology, thus including moderate and severe TM retractions, cholesterol granuloma, granulation tissue, bone erosion, invasive tympanosclerosis and silent chronic otitis media. COM can be also sub-classified into two major groups: COM with cholesteatoma (CCOM) and COM without cholesteatoma (NCCOM).

TM perforations can vary in size and appearance. Costa and Rosito used to classify TM perforations into inside-out (IOP) and outside in (OIP). While IOP are mostly central and kidney shaped, OIP present signs of a previous TM retraction. Stretching the concept we would even dare to affirm that IOP represent a disease of the TM while the OIP are truly one of the most apparent sub-products of a disturbed homeostasis and physiological imbalance of the middle ear.

Hearing loss associated with this pathology usually is conductive and can vary considerably in severity. This variation correlates directly to several sub-factors: size and position of the TM perforation, degree of ossicular fixation, presence of major or minor ossicular erosions, ossicular dislocation and, obviously, the repercussion of all this process in the inner ear. In a study that included children and teenagers, was found a positive association at all frequencies between the number of quadrants affected by TM perforation and the conductive hearing loss (measured by the air bone gap) [26].

The sensorineural hearing loss has been associated to NCCOM, although the real impact of it is still object of research. Using the normal contralateral ear as control in patients with COM, we observed a statistically significant difference between the average bone conduction thresholds of ears with COM and their contralateral ears for all frequencies. Despite being statistically significant, however, this difference may not be clinically relevant, since changes of 5 to 10 dB on tonal audiometry do not represent an important hearing loss, nor does it imply any change in treatment plan, such as indicating use of a hearing aids [27].

TM retractions are special conditions. Whereas they may present as an incidental finding or with minimal symptoms, clearly they represent irreversible tissue pathology (TM atrophy and ossicular erosion) and a potential for cholesteatoma formation.



Figure 3. Illustration of a NCCOM, with severe retraction of the TM and fixation of the ossicular chain. (Image of the Department of Otolaryngology-Head and Neck Surgery, Hospital de Clinicas de Porto Alegre)

A recent study of Schmidt et al. demonstrated that severe *pars tensa* retractions with incus erosion and TM adhered to the stapes (tympanostapedopexy) were associated with small air bone gaps (<25 dB) in 85% of the patients. In other words, this kind of situation usually works as a nicely performed natural type III tympanoplasty. So, the need for a tympanoplasty to improve the auditory function in these cases is not recommended.



Figure 4. Illustration of a TM perforation. (Image of the Department of Otolaryngology-Head and Neck Surgery, Hospital de Clinicas de Porto Alegre)

4. CHRONIC OTITIS MEDIA WITH CHOLESTEATOMA

Cholesteatoma is the most aggressive spectrum of chronic otitis media (COM). It is a progressive disease that causes hearing loss and recurrent otorrhea. Cholesteatoma is characterized by the accumulation of exfoliated keratin debris in the middle ear or other pneumatized areas of the temporal bone [28]. Since cholesteatoma was first described, many classifications have been proposed. In principle, it is accepted that cholesteatomas can be classified into two categories: congenital and acquired [29]. As congenital cholesteatomas are very rare, the existent classifications are applied to the acquired type. The classifications are based on otomicroscopic appearance [30], typical growth patterns [31], disease extension [32], surgical findings [28], and otoscopic drum status [33].

Hearing loss is one of the more disturbing symptoms in patients with cholesteatoma. In our previous study, we found that hypoacusis and otorrhea were the main complaints of most patients, and 87% had otorrhea at the time of evaluation. Complaints of hearing loss were confirmed by audiometry, which showed that the vast majority of patients had conductive hearing loss with larger air-bone gap of 20 dB in speech recognition area. [34]

We also demonstrated that, compared with posterior epitympanic cholesteatomas, posterior mesotympanic cholesteatomas had greater (air bone gap) ABG thresholds at 500 Hz, 2000 Hz, and ABG PTA (pure-tone average), which correspond to the speech reception frequencies. The two growth patterns, however, were very similar with regard to the other audiometric parameters. In children, no audiometric differences were found between the two groups, whereas, in adults, compared with posterior epitympanic cholesteatomas, posterior mesotympanic cholesteatomas showed higher AGB thresholds at 500 Hz to 3000 Hz and higher ABG PTA, in addition to higher AC thresholds at several frequencies. [35]

When we studied the sensorineural hearing loss in cholesteatoma, we found that the cholesteatoma ear was associated with greater (bone conduction) BC thresholds than the (contralateral ear) CLE. The presence of cholesteatoma in the middle ear was associated with greater BC thresholds at all frequencies tested, when compared with the normal CLE. These BC differences were observed both in children and adults, and independently of

cholesteatoma growth pattern. The frequency of labyrinthine fistula in our sample was low, and thus it may have little influence in the global sensorineural hearing impairment associated with cholesteatoma. The correlation between the air bone gap media in the ear with cholesteatoma and the difference in bone conduction thresholds between both ears was direct and moderate. In other words, when more damaged the tympanossicular system is, greater the sensorineural deficit will be [36].



Figure 5. Illustration of a posterior mesotympanic cholesteatoma. (Image of the Department of Otolaryngology-Head and Neck Surgery, Hospital de Clinicas de Porto Alegre)



Figure 6. Illustration of an attical cholesteatoma. (Image of the Department of Otolaryngology-Head and Neck Surgery, Hospital de Clinicas de Porto Alegre)

An understanding of the different types, behavioral patterns, and hearing impairment caused by cholesteatomas will enable us to improve the prognosis of this disease by optimizing its treatment and improving surgical techniques for both complete removal of the pathological tissue and successful reconstruction of the damaged ossicles. We also believe that a better understanding of the sensorineural damage associated with cholesteatoma cannot

be overstressed. It is quite obvious that all these changes are time-related, so, in our opinion, it is very important to monitor these patients very closely in order to decide for a surgical intervention during the earlier phases of the disease. In doing so, we may abort the natural history of cholesteatoma and its deleterious consequences. To define with precision the surgical timing for carrying out such an intervention is still a matter of great debate, but it seems plausible that during the early phases surgeries may be less aggressive and residual function is maintained. The preservation of an adequate inner ear function is of paramount importance especially nowadays with the development of new prosthesis and the advent of bone anchored hearing aids and actives middle ear implants specifically indicated for patients with COM. This knowledge may assist the development or improvement of new technologies, and may be of even more benefit with regard to BC than our demonstration that SNHL (sensorineural hearing loss) may be present in most patients with cholesteatoma, and that this damage can be clinically relevant in several cases.

5. CHRONIC OTITS MEDIA TREATMENT

5.1. Tympanoplasty and Ossicular Reconstruction

Tympanoplasty is the procedure of choice in the treatment of tympanic membrane perforation. It is the first step in the resolution of hearing loss by the reconstruction of the tympanum with temporal fascia, tragus cartilage or other kinds of enxerts. Is still controversial the ideal time to perform tympanoplasty in children. The recommendation is around 7 or 8 years, when the child is more collaborative and the otitis media episodes ussually slow down. However, several groups around the world perform tympanoplasty in children ealier, with good results. The approach can be transcanal, retroauricular, and, more recently, transcanal with the use of microscopes. James has demonstrated that use of endoscopes in children is safe, providing good results, excellent visibility of all perforation without necessity of canaloplasty and with no big scars and little pain.

Tymanoplasty is also the last step in cholesteatoma surgery. The surgeon may choose between open or closed mastoidectomy, but tympanoplasty will be always performed if the surgeon sucessfully removed all the epithelium of the middle ear and mastoid.

One of the complications caused by chronic otitis media with or without cholesteatoma is ossicular discontinuity.

The goals of the COM management are auditory rehabilitation and disease eradication. This rehabilitation is usually performed during second look surgery in children, through the ossicular reconstruction [37].

Nowadays, the most used material to compose the prosthesis on ossicular reconstruction is titanium, [37] and partial ossicular replacement prosthesis (PORPs) is more used than total ossicular replacement prostheses (TORPs). [38] Probably this is because good auditory results are more frequent in partial ossiculoplasty compared with total ossiculoplasty, and the displacement of TORP is bigger than PORPs in children [37].

Murphy at al. compared hearing results after ossicular reconstruction with PORPs and after ossicular reconstruction with TORPs in pediatric patients with COM. They found that

children who underwent ossicular reconstruction with PORPs had slightly better postoperative hearing than children with TORPs [38].

In studies with adults, a few predictive factors for postoperative results in ossicular reconstruction have been illustrated, like persistent or recurrent abnormalities within the middle ear, presence of a malleus handle and preoperative middle ear mucosa status. Nevoux et al, in 2011, evaluated predictive factors of a good outcome with the use of a total ossicular replacement prosthesis in children and demonstrated that preoperative average air-bone gap and the footplate status are predictive factors of the results of ossiculoplasty [37].

A study of Jeng et al, in 2003, demonstrated preoperative findings that are related to status of the ossicular chain at surgery. Three parameters should be considered feasible predictors of ossicular discontinuity in COM: cholesteatoma extension into the tympanic sinus, persistently draining ears (cholesteatoma group) and perforation edges adherent to the promontory (noncholesteatoma group) [39].

5.2. Bone – Anchored Hearing Aid and Cochlear Implant

Since the introduction of the bone anchored hearing aids (BAHA) at the market in the 1980s, it became a common treatment of conductive hearing loss in patients who failed with the conventional air-conduction aid, in congenital malformations of the external and middle ear, chronically discharging ear, conductive hearing losses attributable to ossicular disease [2]. It is suitable because the sound is transmitted directly to the cochlea through the cranium, circumventing any external or middle ear anomaly or pathology.

A study conducted in Canada with 12 specialists, showed that congenital aural atresia was identified to be an indication for pediatric BAHA for all professionals who perform that kind of surgery, other common indications for this procedure were: chronic otitis externa or media with hearing loss (92%), allergic reactions to conventional hearing aids (75%), congenital fixation or anomaly of the ossicular chain (67%), and unilateral deafness (25%). The use of BAHA in this last population is mainly to establish binaural hearing, but the audiological benefits are variable [40]. Priwin et al. noted an improvement of speech recognition in noisy environments without improvements in hearing thresholds or sound localization [41]. Despite its inconsistencies, BAHA in children with unilateral hearing loss have been found to have a positive impact of quality of life with high rates of user compliance.

Watson et al. used the validated Glasgow Benefit Inventory (GBI) to assess changes in general, social and physical health benefits (quality of life benefits) of patients who were fitted with a BAHA for different conditions and then separated them in subgroups (neuroma acoustics, discharging mastoid cavities, chronic active otitis media, otosclerosis, congenital atresia). The patients that were submitted for a BAHA because of congenital atresia scored the best improvement in quality of life, this could be explained by the fact that these patients don't compare their improvements with what they had in the past and consider it as a benefit [42]. Despite that, the subgroup that gained more physical benefits than the others was the chronic active otitis media, it could be explained by better ventilation and a dry ear, while still delivering continuous sound amplification when compared with the conventional air-conduction aids.

One of the main benefits of the bone-anchored hearing aids is the use in mixt hearing loss. In these cases, patients can achieve normal hearing even if they have bone conduction thresholds around 55 dB.

Rarely patients can present profound bilateral hearing loss as a consequence of chronic otitis media. In these cases, cochlear implant surgery is the best option of treatment as soon as the resolution of inflammatory process occurs. In cholesteatoma cases, it is recommend that the cochlear implant surgery would be performed after 6 or more months from cholesteatoma surgery. Some centers prefer to perform a petrosetomy with cavity obliteration prior to cochlear implant surgery.

6. IMPACT OF CONDUCTIONAL HEARING LOSS IN LANGUAGE DEVELOPMENT

The presence of hearing loss in the first few years of life can have an impact in language development [43-46]. Considering that children learn speech and language from listening to other people talk, it seems critical to have an optimal sensorial input in this period.

Otitis media with effusion presents a special problem because symptoms of pain and fever are usually not present. Therefore, weeks and even months can go by before parents suspect a problem. During this time, the child may miss out on some of the information that can influence speech and language development. Parents should pay attention on some signs like inattentiveness, wanting the television or radio louder than usual, misunderstanding directions, listlessness, unexplained irritability, and pulling or scratching at the ears, because they may indicate chronic or recurring fluid in the ear [47].

Despite the conceptual logic of the hypothesized relationship between OME and language impairment, there is not a consensus about the studies findings. It is important to consider that many variables related to hearing loss can interfere in the language acquisition. Roberts et al. (1998) pointed out four important reasons to this misunderstood. First, few studies have examined hearing loss as an independent variable, instead they use OME as the predictor variable. However, the degree of hearing loss associated with OME is not constant; some children experience no loss and other children a moderate loss as great as 50 dB HL [48]. Second, previous studies have not considered recent models of child development that emphasize the transactional and multifactorial nature of development, particularly the importance of the caregiving environment. Considerable research supports the influence of a responsive style of interaction by parents and by child-care providers in child-care programs in facilitating children's language development. Third, few studies have examined whether certain periods of development were particularly sensitive to language difficulties because of OME. It is possible that specific periods, such as when children are acquiring the sound symbol associations of their native language during the first year of life, may be more vulnerable to language difficulties than later periods when children are expanding their vocabulary and sentence length. Fourth, the dependent measure of language development in previous studies has been measured broadly (eg, receptive language or expressive language), and may not be sensitive to the specific effects of OME and associated hearing loss. Specific language competencies (eg, vocabulary acquisition and language use) also need to be examined when looking for OME sequelae.

Aiming to contribute with this last concern, Borg et al. (2007), create an reference material based on the total population of the Swedish hearing-impaired children at the age of 4—6 years, who had up to 80 dB HL hearing threshold in the best ear, whose first language was and spoken Swedish (and not signed) and who had no other diagnosed major handicaps. The reference material analyzes different language aspects and have a healing methodological design and statistical analysis [49]. Like this, another studies have to be done to contribute with the comprehension of the impact of OME in the language acquisition, considering child age, effusion duration, different languages, socioeconomical status and different aspects of language (always affiliated with a clear theoretical background).

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Chapter 50

BINAURAL, SEQUENTIAL OR SIMULTANEOUS COCHLEAR IMPLANTS IN CHILDREN: A REVIEW

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ABSTRACT

The early detection of hearing loss, as well as the early appropriate intervention, is critical for proper language, relational and cognitive development. Hearing loss in children can be congenital or acquired. It can be classified in prenatal, perinatal and postnatal, considering the time of occurrence, and it can be transitory or permanent. The worldwide estimated prevalence of hearing loss is 1/1000 for children without risk factors for hearing disease, 2-3/100 for those with risk factors. The prevalence of prelingual hearing loss in Italy is reported in 0.7/1000 within the Italian population [1].

Cochlear Implants (CIs) are considered a safe and effective method for rehabilitation of profound hearing loss in infants [2, 3], and particularly in children, bilateral cochlear implantation is becoming gradually more common in clinical practice. The advantages of bilateral hearing are well known; nonetheless, while among the adults, the benefits of bilateral implants have been previously established [4], the data available among children are still limited.

Aim of the present chapter is to discuss and evaluate the effectiveness of the application of bilateral CIs in children, either sequentially nor binaurally, affected by profound/severe sensorineural hearing loss.

Keywords: hearing loss in children, cochlear implants, language development, pediatric neuroradiology

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INTRODUCTION

Hearing loss in children can be congenital or acquired and it can be classified in prenatal, perinatal and postnatal, considering the time of occurrence. The worldwide estimated prevalence of hearing loss is 1/1000 for children without risk factor for hearing impairment and 2-3/1000 for those with risk factors [5]. The prevalence of prelingual hearing loss in Italy is reported to be 0.7/1000 within the Italian population [1].

The early detection of hearing loss, as well as the early appropriate rehabilitative intervention, is critical for the developing of proper language, relational and cognitive skills [6].

Since the implementation of newborn hearing screening programs, nowadays it is possible to early recognize moderate to severe hearing loss. It has been recommended to perform the screening within the first month of life [6, 7]. Even if not all forms of hearing loss can be detected by newborn hearing screening, due to the late onset of some sensorineural hearing loss, the reported average age of diagnosis of hearing defects (bilateral moderate-to-severe hearing loss) and intervention in children is lowered from 26 and 32.2 months, respectively [8], to 2 and 4 months of life, since the publication of the Joint Committee on Infant Hearing statement in 2000 [9, 10, 11]. It is clear that this first period of life is decisive for the acquisition of acoustic stimuli and therefore for a regular development of central auditory pathways; the correction of hearing loss is necessary since the early age. Language development starts at birth with detection and discrimination of sounds and culminate at 8-12 months, when the linguistic and communicative skills are already settled [12, 13].

In 2013, the American Academy of Audiology [14] described the characteristics of paediatric amplification, according to hearing loss level and prosthetic technology available, in order to guarantee a correct development of verbal production and learning abilities. Therefore, a prompt therapeutical-rehabilitative program is recommended by hearing aids in those children affected by moderate hearing loss and by cochlear implant in those affected by severe/profound hearing defect.

COCHLEAR IMPLANTS (CI)

Cochlear implant (CI) is a medical electronic hearing device for auditive rehabilitation in case of severe-to-profound hearing loss, that is available also for infants and children. The first single-channel CI was introduced by Dr. William F. House in 1961 [15, 16]. Since this first implantation surgery, technologies, processing system and the different parts of the implant have experienced evolutions and improvements, until the current and innovative models.

CI differs from the traditional hearing aids as it is able to substitute the cochlear function, directly providing a stimulation on the acoustic nerve through electrical signals [17]. The acoustic stimulus, received by the microphone, is decomposed in frequencies in the external sound processor and transduced in electrical stimulus (simulating the cochlear function), which is transported by the receiver/stimulator to the electrodes implanted in the cochlea [18]. In the modern multi-channel CI, firstly developed in the late 1970s, the electrode array,

inserted in the scala tympani, is able to stimulate different cochlear areas [17, 19], with the minimum interference between electrodes.

CI INDICATIONS IN CHILDREN

The conventional candidate for cochlear implantation is represented by a patient with bilateral severe-to-profound sensorineural hearing loss (SNHL) and who experiences poor advantages from traditional hearing aids [17]. Recently, the FDA (Food and Drug Administration) revised the criteria for pediatric cochlear implantation [20], approving surgery also in children younger than 2 years, in case of profound bilateral SNHL and in children older than 2 years, in case of severe-to-profound bilateral SNHL. In older children (> 4 years), CI could be proposed in any case of severe SNHL whenever the child does not progress in speech and language abilities, just by using traditional hearing aids [21].

Since language learning starts in the first months of life, there is a temporal window during which is necessary to intervene in children, in order to rehabilitate the hearing function. Those children early diagnosed with a profound bilateral SNHL have to be implanted as early as possible, between 12 and 24 months of life, also as the reported incidence of postoperative complication is low [22]. In these children it has also been proposed to perform a bilateral cochlear implantation, simultaneous or sequential [22]; binaural stimulation is crucial for spatial orientation and sound localization, particularly in a noisy environment [3]. Since the second half of 1990s, bilateral cochlear implantations has been performed always more frequently, also considering the fact that in case of malfunction of one device, also the other ear is implanted [3]. Audiologists, but also speech therapists, teachers, patient family members, are all involved in the rehabilitative strategy, following implantation and during the follow-up.

However it is possible to restore binaural hearing not only with bilateral hearing aids or bilateral cochlear implants, but also with a bimodal stimulation. In monolateral implanted children, it is always advisable, when possible, to pursue a bimodal stimulation in case of residual hearing in the contralateral ear, then still offering important advantages to the little patients [23].

CIS IN CHILDREN WITH INNER EAR MALFORMATIONS

Inner ear malformations are not frequently implanted, but represent about 20% of congenital SNHL, both sporadic and syndromic forms [24]. In inner ear malformations undergoing cochlear implantation, medical imaging is even more important, both for etiologic diagnosis and for pre-surgical evaluation. CT (computed tomography) study of temporal bone is essential to highlight possible anatomic alterations of the facial nerve course that the surgeon should aware. It is also necessary to evaluate the width of internal auditory canal (in order evaluate the presence of a VIIIth nerve hypoplasia) and a labyrinth or cochlear aplasia; only the latter represent a contraindication to CI. Furthermore, CT can show cochlear calcification and/or a reduction of round window size, which may compromise the correct

insertion of CI [25]. MRI (magnetic resonance imaging) of the brain allows to analyze directly the acoustic nerve course and the labyrinthine fluids.

In infants presenting a common cavity or incomplete cochlear partition (IP) as IP-I and IP-III, according to the classification of Sennaroglu and collaborators [26, 27], it has been recommended to perform a CI as early as possible, as frequently this kind of malformations have been reported to not to benefit from traditional hearing aids [24].

With the exception of common cavity or hypoplastic cochlea, in which the poor representation of neural cells could determine insufficient functional outcomes, data in literature report that implanted children with inner ear malformations undergo the same results of implanted children with normal anatomy, considering both the sound perception and the language development [28].

CI IN CHILDREN AND OTHER DISABILITIES

The application of hearing aids and, even more, of CIs in children with hearing loss associated to other disabilities is a very complex choice as the rehabilitative process could result not adequately efficient compared to hearing impaired children without disabilities [29]. About 30-40% of children with hearing impairment shows disabilities associated, and in many cases it could be very difficult to predict post-implantation functional outcomes, particularly as also the audiologic and neuropsychiatric pre-implant evaluations can be not conclusive [30]. But, differently from the past, in the last 20 years an increasing number of multi-handicap children have been implanted, as, by now, it is reported that also these categories of little patients can benefit from electric hearing rehabilitation. The functional results of CI are not just limited to the verbal performances and language abilities, as CIs can also influence the global behavioral adjustments, the social development and integration with the environment, also having implications among quality of life of these children [31]. Pre-implantation cognitive level has been reported to represent one of the most significant and reliable benefit predictive factor for CI outcome in these children [32]. Severe mental retardation, severe autistic disorders and psychiatric disorders with auto-aggressive behavior represent conditions that need an accurate pre-implant analysis, because they are frequently correlated to failure.

BILATERAL CIs IN CHILDREN

Before the 1990s, CI was generally performed unilaterally, considering also the economic aspects. In 2007, Murphy and O'Donoghue stated in their review [3] that pediatric bilateral cochlear implantation determines better auditive abilities, both in noise and in sound localization, compared to the functional outcomes of monolateral implanted children, probably due to the head-shadow effect.

Even if data in literature don't show significant functional differences between simultaneously and sequentially bilaterally implanted adults [33], there are data supporting the fact that children undergoing an early bilateral simultaneous implantation show better speech recognition and language development, compared to children with sequential bilateral

implantation [34, 35]. Furthermore, it is well known that there is a critical period for the binaural system development, due to the cerebral plasticity of the first months of life and the auditive experience. In fact, data in literature show worst functional results in sequentially bilateral implanted children, with the second CI introduced with a delay, after this critical temporal window [36, 37, 38].

The gold standard for a harmonious language and cognitive development is represented by cochlear implantation under or around 12 months of life [20, 39, 40, 41], even if, by now, there are poor data about this category of candidates for CI and comparative studies between implanted children are challenging and scarcely significant, primarily because of an insufficient follow-up and of a lack of homogeneity of the verbal perception and production evaluations in so little children.

CONCLUSION

CI is still an expensive therapeutic solution, in consideration of the advanced implant technologies and the continuous evolution of the speech processor, the receiver/stimulator and the electrode array. Nonetheless, CI has a so relevant impact on the quality of life that, on the whole, it represents a crucial cost-effective device for hearing impaired children [22].

It is likely that, in the future, other treatment could be available (i.e., inner ear regenerative approaches by stem cell or genetic therapy); also in this view, some authors still have some concerns when indicating a bilateral CI. However the possible benefits of restoring binaural hearing should be carefully taken in consideration.

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Chapter 51

VIRTUAL REALITY FOR COCHLEAR IMPLANT SURGERY

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ABSTRACT

The ultimate surgical steps of cochlear implantation are facial recess approach and an insertion of the electrode through the cochleostomy which require repetitive practice to acquire the appropriate skills before entering the operating room. However, the human cadaveric temporal bones are a scarce resource. This problem limited the trainee chance to practice to the optimum level.

Virtual reality has been introduced to the medical field and is now used in medical education as an alternative high fidelity simulator. Many studies have found that virtual reality simulators have improved the operative performance of the trainees. The major components of successful learning that has contributed to the efficacy of the virtual reality system are the ability to provide repetitive practice under a controlled environment, self-directed learning and proved for a construct validity.

The author of this chapter is a surgeon and developer of the surgical virtual reality system of the temporal bone based in Melbourne, Australia, which is the only institute that located in the Asia-Oceania region. He will share his expertise on the future of this virtual reality to maximize the goal of cochlear implant surgery.

Keywords: otolaryngology, surgery, planning, virtual reality

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INTRODUCTION

Current advances in the computer-generated virtual environment, namely virtual reality (VR) has enabled us to simulate the training environment for surgical education. Surgical training in human subjects has the aim for perfection. Any untoward errors, intend or not intend, are not acceptable. Unlike the practice on non-human, this can be done with the freedom of perfection. The surgeon usually needs to pass the certain amounts of practices on non-human models or cadavers to ensure that their skills were close to perfection and ready to practice on the patients.

The proper training configuration to improve the surgical skills such as psychomotor and technical skill is essential for excellent surgical outcomes and safety of the patients. Virtual reality can simulate the complex surgical procedure, including temporal bone surgery and cochlear implantation. Virtual reality offers the attractive possibility for the novice, surgical trainee, and experienced surgeons. The novice and surgical trainee can acquire core competencies and dexterity in the training platform without doing harm to the patient. On the other hands, the experience surgeons can use the virtual reality platform as the surgical planning tool in complicated surgical procedures.

This chapter will explore the current evidence of the virtual reality platforms as the surgical training tool for cochlear implant surgery and associated procedures.

WHAT IS THE VIRTUAL REALITY SIMULATION?

Surgical training is a field of specialization that is heavily reliant on the model of apprenticeship. Traditionally, surgical residents are required to operate on a pre-defined number of cases under the supervision of his/her mentor. With recent legislation limiting the working hours of surgical trainees, exposing them to an adequate number of cases has become a non-trivial issue. Limited training hours combined with the need to serve a growing population has resulted in calls for a more efficient program of surgical education. Within this context, simulation has emerged as an important platform for which medical education programs are developed.

Simulation is an ideal medium in which principles of adult learning can be effectively embodied [1]. While some of these principles are easily accomplished through the traditional mentor-mentee model of surgical training, others, such as the need to match the teaching technique to the diversity and background of the trainee may be harder to achieve, as it is usually dependent on the style of instruction of the mentor. Further, with simulation, it is possible to allow trainees to be actively involved in the surgery at an earlier stage of learning without undue risk.

Virtual reality simulation is the combination of computer-generated environments with tactile, auditory and visual stimuli that promote increased authenticity [2]. It supports one of the major principles of skill acquisition: deliberate practice [3] - goal oriented, repeated performance that allows trainees to refine their skills and appreciate variations in the way a single activity is constituted. Figure 1 shows the three-dimensional model from the virtual reality system.

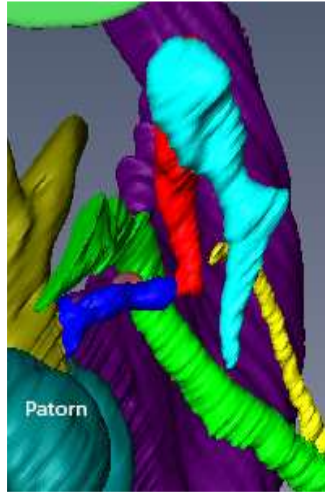


Figure 1. Three dimension model of the malleolus, incus, and stapes.

Virtual reality simulation-based surgical training is fast becoming an attractive area of research [4-6]. For example, Madan and Frantzides [7] compared virtual reality laparoscopic training with box trainers and no training and found that the post-training score in the virtual reality group was significantly higher. Rose and Pedowitz [8] observed that virtual reality arthroscopic training improves the skills of trainees. Palter and Grantcharov [9] showed that deliberate individualized practice on a virtual reality simulator improves the technical performance of surgical trainees in the operating room for laparoscopic cholecystectomy. Gala et al. [10] observed that the technical skills of residents performing laparoscopic bilateral midsegment salpingectomy trained on a simulator were higher than those taught using traditional teaching methods.

CHALLENGES IN SURGICAL TRAINING

The surgical skills are complex and can be divided into technical and non-technical skills. Technical competencies in the operating theater included psychomotor skill (physical coordination providing precise movement), procedural skill (task accomplishment through a sequence of actions), and surgical anatomy skill (knowledge of specific anatomical structures). The non-technical competencies in the operating theater included situational awareness skill, decision-making skill, communication and teamwork skill, and leadership skill. Non-technical skills are equally important for achieving good surgical outcomes. Non-technical skills can be broadly classed as those required to make the correct decisions at the right time during an operation, and those required to integrate and lead the operating room team [11].

In the current apprenticeship model, the mentor starts as a role model for the trainee to observe. Under the mentor's discretion, the mentor will gradually change to a coach who guides the trainee towards competency. The surgical trainee is provided with increasing challenges and subsequently achieves the capability for the articulation of the procedural

steps. Lastly, expertise arises from reflection and the ability to explore and invent new strategies [12].

For patient safety, the mentor needs to ensure that residents have appropriate capabilities before practice on patients. While this practice has served the medical community well over the years, it has not been entirely devoid of problems. One of the major issues is insufficient numbers of patients creating a lack of suitable cases for teaching, resulting in inadequate exposure to scenarios trainees may encounter. Other problems are the restrictions on working hours limiting the available time for training and the increased awareness of patient, quality and safety issues.

Many of these challenges, resulting in increasing specialization, discontinuity in patient care, and an increasing duration of training as consequences [13]. It is clear that the future surgical training program can no longer rely on the apprenticeship model only. The virtual reality may be the useful tool adjunct to the future training program.

VIRTUAL REALITY SURGICAL TRAINING

In the current surgical training program, several training methods were introduced for better learning outcomes, including lectures, live or video-recorded demonstration, computer assisted learning, and simulation-based learning. Cadaveric dissection has been the standard surgical simulation training method since the start of modern medicine. However, due to the restraint resource of cadaver availability, the inanimate objects such as mannequins, simulated patients and more recently, virtual reality surgical training systems were developed.

Cook et al. [14] conducted the review on technology-enhanced simulation training for health professional learners. They found the large effects on the results of knowledge, skills, and behavior, and with moderate effects on patient-related outcomes when using the technology-enhanced simulation. The high-fidelity medical simulations such as virtual reality can facilitate learning under the right conditions. The recent studies integrate the simulation-based exercises into the standard medical school or postgraduate educational curriculum. The results suggested an essential feature of their efficient use, including a range of task difficulty level, multiple learning strategies, capture clinical variation, controlled environment and individualized learning [15].

Table 1. Features and uses of medical simulations that lead to effective learning

Features of Simulations (in order of importance)
1. Feedback is provided during the learning experience.
2. Learners engage in the repetitive practice.
3. The simulator is integrated into the medical curriculum.
4. Learners practice with increasing levels of difficulty.
5. The simulator is adaptable to multiple learning strategies.
6. The simulator captures clinical variation.
7. The simulators are embedded in a controlled environment.
8. The simulator permits individualized learning.
9. Learning outcomes are clearly defined and measured.
10. The simulator is a valid (high-fidelity) approximation of clinical practice

Issenberg et al. [15] and McGaghie et al. [16] have proposed features that should be included in a simulator for effective skill acquisition (Table 1). Many surgical simulators have been based on these principles, so as to optimize their educational value [17, 18].

The simulation-based training can augment with the current apprenticeship model by allowing for repeated and deliberate practice for optimal skill development that can map onto the real-life clinical situation. Although simulation-based training has fewer of the time and safety-related constraints compared with the surgical apprenticeship, implementation into the surgical curriculum infrequently considers the individual and timely need of the trainee. Instead, simulation-based skills training is often organized as intensive courses, boot camps, and similar, isolated, single-instance training opportunities. From an educational point of view, this can result in simulation-based training being uncoupled from the trainees' everyday work and the transference of the acquired skills to clinical practice can, therefore, be a challenge [19].

TRAINING IN TEMPORAL BONE SURGERY

Temporal bone dissection is the essential and standard practice for current Otolaryngology – Head and Neck Surgery residency training programs worldwide. Temporal bone dissection will form the anatomical basis and the relation of the temporal bone structure such as mastoid, middle ear, and inner ear. During the temporal bone dissection, the trainee will collect the surgical skills experience including drill handling, operating microscope use, suction and irrigation, and knowledge of surgical procedural steps. The dissection is usually done under the supervision of the instructor both in temporal bone dissection workshop or temporal bone laboratory.

The temporal bone dissection workshop was designed for the residents who have minimal or no experience with temporal bone. The course often includes lectures, video demonstrations, and temporal bone drilling on cadavers and/or simulated temporal bones. Currently, there was a cochlear implantation workshop which will cover the surgical technique and electrode insertion guidelines. Participants will have their workstation and specimens ranging from cadaveric to three dimensions bone models highlighting different anatomies and patient age groups.

The drilling of human cadaveric temporal bones closely mimics real life conditions, including the variable pneumatization of the temporal bone. However, temporal bone lab facilities need high maintenance costs and limited availability of cadaveric temporal bone. The temporal bone workshop is also facing the problem of operating cost. The workshop requires the experience and well-known faculties to attract the trainees. For a reason above, this limited the trainee opportunity for optimal practice.

Many authors have addressed these problems and the proposed use of alternative simulators that can replace or augment training for cadaveric temporal bone dissection, which ranges from simple models to virtual reality simulators [20-22]. Some authors prefer bony models to practice temporal bone dissection surgery [22], but the majority prefer virtual reality systems. Beside of temporal bone dissection simulators, some authors have also developed the middle ear surgery simulator for myringotomy [23, 24] and benign paroxysmal positional vertigo treatment [25].

VIRTUAL REALITY TEMPORAL BONE SIMULATORS

Current Systems

The VOXEL-MAN TempoSurg simulator is the first commercially available temporal bone virtual reality simulator [18]. Volumetric high-resolution computed tomography images of the temporal bone are used to produce a 3-dimensional representation. The surgical site is displayed in stereoscopic mode, which the user views through shutter glasses. Vital structures are color-coded. The station houses a computer with software that is linked to a force-feedback hand stylus. This stylus serves as a virtual drill, which is activated by the foot pedal to alter the appearance of the virtual temporal bone. The drill responds to forces, according to the contact situation visible on screen, allowing the user to experience changes in pressure. The computer records its location, direction in space, and some performance measures such as excessive force or injuries relating to vital structures. The user can alter the surgical orientation, drill size, type, and rotation speed.

Another commercial model of the temporal bone dissection simulator is the Mediseus Surgical Simulator (CSIRO/University of Melbourne temporal bone simulator). This simulator consists of a simulated operating microscope. The user interacts with a 3-D volumetric virtual rendering of a cadaver temporal bone, which is controlled by the surgeon using two haptic motorized 3-D pointing devices. These devices allow the computer to track the exact movement of the tool relative to the virtual bone model. The bone model was given color and hardness properties to provide visual and tactile cues that helped to simulate real operating conditions. The coloring of the bone also changes as the bone is progressively thinned over the critical structures such as the sigmoid sinus, dura, and facial nerve. Physiological functions, such as bleeding from the sigmoid sinus and facial nerve monitoring with auditory and visual feedback were also built into the simulator [26].

Many ear surgery simulators are currently under development [27-29]. They mostly share common features of haptic feedback. Some of them also work with acoustic feedback.

Validity of Simulator Systems

For face and content validation, the VOXEL-MAN TempoSurg simulator group recruited 25 Otolaryngologists and 60 trainees. They found that the familiarization took longer in the experienced group ($p = 0.01$) but user-friendliness was positively rated. Seventy percent of participants rated anatomical appearance as acceptable. Trainees were more likely to recommend temporal bone simulation to a colleague than trainers ($p = 0.01$). The transferability of skills to the operating room was rated neutral by the participants [18].

To evaluate the construct validity, the Mediseus Surgical Simulator group recruited a total of 27 participants for the study. Twelve of these participants were Otolaryngology surgeons, 6 were residents, and 9 were medical students. The authors found that the experts completed the simulated tasks at significantly shorter times than the other two groups (experts mean 22 minutes, residents mean 36 minutes, and novices mean 46 minutes; $p = 0.001$). Novices were more likely to injure structures such as the dura compared to experts (23 injuries vs. 3 injuries, $p = 0.001$) [26].

Efficacy of Simulators on Skills Improvement

The VOXEL-MAN TempoSurg simulator group [30] conducted a before-after investigation and found that some surgical skills that were evaluated based on the Objective Structured Assessment of Technical Skills (OSATS) exhibited a significant improvement after practices were conducted by using the virtual reality temporal bone simulator system. The OSAT scores were improved for both tegmen task from 2.125 to 3.1 ($p = 0.026$) and sigmoid task from 2 to 2.75 ($p = 0.0098$). The time to complete the tasks also decreased from 8.37 to 5.39 minutes ($p = 0.018$) for tegmen task and from 8.99 to 8.68 minutes ($p = 0.594$) for the sigmoid task.

The Mediseus Surgical Simulator from University of Melbourne's virtual reality research group did further research on the improvement in the users' skills by conducting controlled trials comparing the simulator training with the standard textbook based training. They found that the participants trained on the simulator performed significantly better than the participants trained using conventional training methods [20, 21]. The experts were invited to review the participant's task through a sequence of actions (procedural score). They found that the virtual reality group performed better than conventional training group (Table 2).

Also, for procedural skill evaluation, the authors [20, 21] also inspected the dissection results by evaluating the end-product temporal bones.

The end-product score represents the combination of anatomical knowledge, procedural skill and psychomotor behavior. They found that the virtual reality group performed better than conventional training group, but there was no statistically significant difference (Table 3).

The virtual simulation for temporal bone dissection group (17, 31) conducted a controlled trial comparing the virtual reality temporal bone dissection training simulator with the cadaveric temporal bone dissection training. Two studies involving 92 participants used the 35-item Welling scale to determine end-product scores for the virtual reality group and cadaveric temporal bone dissection training group. There was no statistically significant difference between virtual reality group and cadaveric temporal bone dissection training group (Table 4).

Table 2. Comparing the procedural score of the Mediseus virtual reality temporal bone dissection training with conventional training

Study	VR ^a Mean (SD)	Control Mean (SD)	Mean difference (95% CI)
Zhao 2011a [20]	3.54 (0.82)	2.51 (0.97)	1.03 (0.24 - 1.82)
Zhao 2011b [21]	3.56 (1.79)	2.97 (1.72)	0.59 (-0.95 - 2.13)

a. VR = virtual reality.

Table 3. Comparing the end-product score of the Mediseus virtual reality temporal bone dissection training with conventional training

Study	VR ^a Mean (SD)	Control Mean (SD)	Mean difference (95% CI)
Zhao 2011a [20]	2.79 (0.79)	1.98 (1.12)	0.81 (-0.04 - 1.66)
Zhao 2011b [21]	3.48 (1.87)	2.64 (1.46)	0.84 (-0.63 - 2.31)

a. VR = virtual reality.

Table 4. Comparing the end-product score of virtual reality temporal bone dissection training with cadaveric temporal bone dissection training

Study	VRa Mean (SD)	Control Mean (SD)	Mean difference (95% CI)
Wiet 2009 [17]	23 (8.6)	17 (8.5)	6.00 (-3.68 - 15.68)
Wiet 2012 [31]	2.2 (0.54)	2.14 (0.56)	0.06 (-0.21 - 0.33)

a. VR = virtual reality.

The results from these studies showed that the virtual reality temporal bone dissection training is more effective than traditional training methods and as effective as cadaveric temporal bones as assessed by the summative end-product score.

COCHLEAR IMPLANTATION

The cochlear implantation is the procedure to restore hearing for deaf or profound hearing loss patients. The procedure itself is highly invasive, and the complications from the operation can lead to dead. The implant device needs some space to fit tightly behind the ear. The mastoid cortex will be drilled out to make space fit the implant device and make the passage access the middle ear. The round window is the anatomical landmark that we usually make the cochleostomy antero-inferiorly to it for the cochlear implant electrode. The electrode insertion is the essential final step. To avoid the trauma to the cochlea, the surgeon needs to be familiar with the anatomy of the cochlea (Figure 2). The proper force and angle of electrode placement will lead to better hearing results. After the electrode was inserted, the cochlear implant device will be tested.

The above surgical step will operate under the microscope as the structures are small and need a delicate maneuver. Throughout this process, there is a risk to introduce trauma to the brain, facial nerve, and vessels. The risk will be increased if the patient has an anatomical variation or change of the normal structure affected by the diseases.

CURRENT TECHNOLOGY FOR COCHLEAR IMPLANT SURGERY

Based on the virtual temporal bone training system for the trainee physicians, which is solely for the educational purpose, the developers step to cochlear implant surgery to make a benefit for the patients. The following technology emerges.

Virtual Guidance for Cochlear Implantation

Hara M et al. have demonstrated the possibility of using the 3D image as a guide to surgery by using preoperative CT images at a slice thickness of 0.5 mm. The inner ear labyrinth, auditory ossicles, and FN were manually shaded in blue, red, and yellow, respectively, maintaining the shape of these structures. The images were converted from colored 2D-CT images to 3D images using the Delta Viewer (DV freeware, Japan).

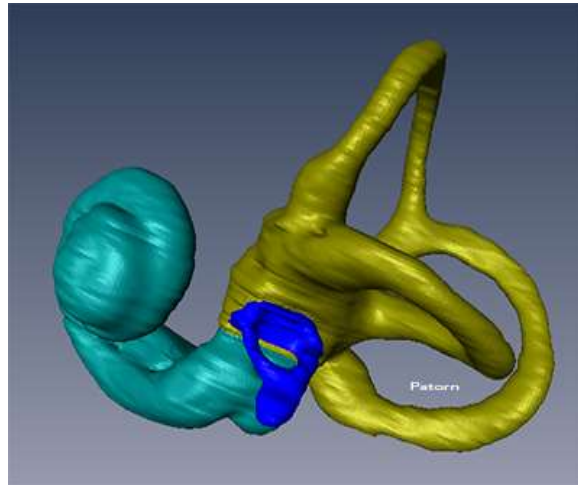


Figure 2. The osseous labyrinth including cochlear.

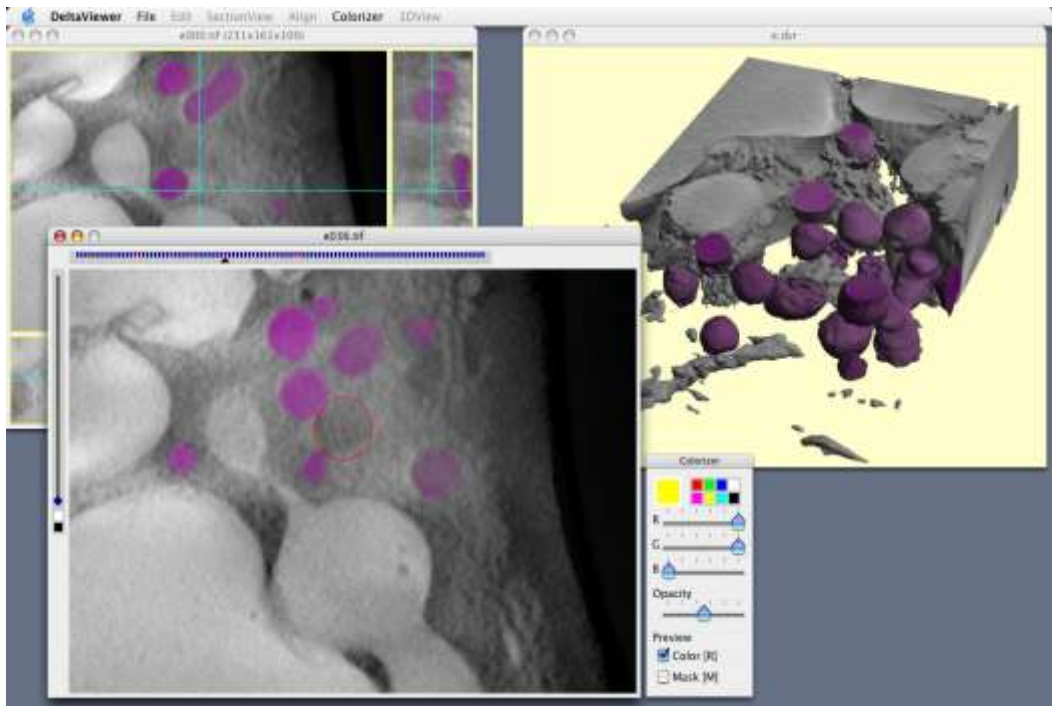


Figure 3. Screenshot from Delta Viewer software.

The authors successfully depict the structures of the inner ear, ossicles, and facial nerve as 3D images, which are very easy to understand visually and intuitively (Figure 3). These 3D images of the malformed ear are useful in preoperative image simulation and surgical planning for those performing a cochlear implant procedure.

Case-Specific Virtual Reality Surgery

The principal aims to make the patient-specific planning before doing the cochlear implant surgery is the patient’s safety and benefit. The virtual reality technology can help the physicians to improve the patient safety by allowing the surgeon to study the individual’s anatomy and perform the virtual surgery under the stress-free environment. For complicated cases, the doctor can test the surgical plan options and learn from the mistake to reach the best surgical approach for each patient. The system can also be used to train the physician trainees to familiar with the operation and surgical anatomy before practicing on the real patient.

The simulator has been used extensively in other fields to simulate the dangerous environment that usually not encounter in the normal activities such as aviation. This principle was applied in the medical field. In cochlear implant surgery, the temporal bone simulator can create the patient-specific three-dimensional model that enables the surgeon to interact freely with the model from the patient-specific data gathering from various imaging sources such as computed tomography (CT) or magnetic resonance imaging (MRI).

The virtual reality surgery system has the potential to be more than just an educational tool in the medical school. It is well established that procedural success in complex tasks is the result of the utilization of adequate technical as well as nontechnical skills. Human factors such as teamwork, situational awareness, communication, and decision-making are vital aspects to ensure a good outcome after any operative procedure [32].

Arora et al. [33] have investigated the feasibility of performing case-specific virtual reality temporal bone simulator at St Mary’s Hospital, Imperial College NHS Trust, London, UK in sixteen participants. Most of the patient found that the case rehearsal could refine the surgical approach in response to individual anatomy. For example, the variant anatomy such as the degree of pneumatization, low-lying dura and high sigmoid sinus influent subsequent task performance. However, case rehearsal of procedures involving the facial nerve and removal of cholesteatoma were not perceived to be feasible on the existing platform due to lack of soft tissue reconstruction and suboptimal depth perception during deeper temporal bone dissection. The summary of the benefits and limitations were demonstrated in Table 5.

The University of Melbourne’s virtual reality team has developed a new auto-segmentation algorithm to overcome the lack of soft tissue reconstruction. Figure 4 below showed the small blue and pink area representing dura mater and sigmoid sinus.

Table 5. Summary of benefits and limitations of case-specific surgical rehearsal and other surgical planning strategies

	Advantages	Limitations
Virtual reality surgical rehearsal	Pre-operative practice Surgical trial for best approach and technique	Cannot rehearse particular procedure due to technical limitation
3D anatomy reconstruction from 2D imaging	Aid 3D conceptual of the anatomy	Less useful for experienced surgeon
2D imaging (CT, MRI)	Surgical planning	Need the conceptual jump from 2D to 3D

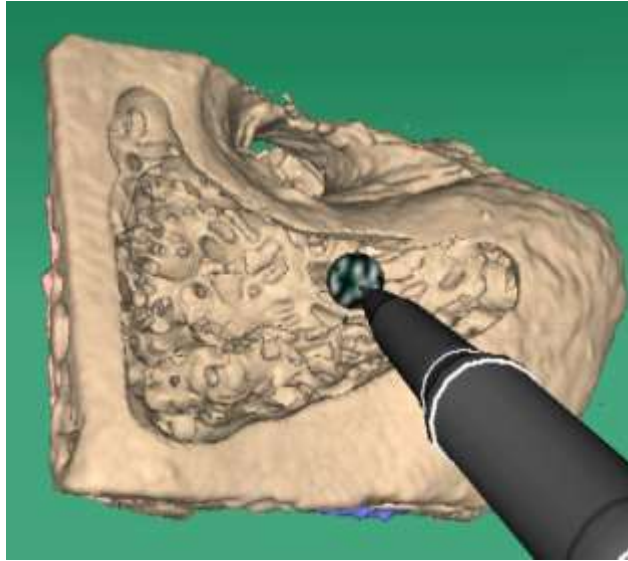


Figure 4. The screenshot from University of Melbourne's virtual reality system.

Real-Time Modeling Electrode Insertion

The electrode insertion is the important step of cochlear implant surgery. The right force administration and correct angle of insertion can be influence the hearing outcome. If the surgeon uses too much force, the electrode can destroy the hair cells and can adversely penetrate the membranous labyrinth that will result in the displacing electrode. The angle of insertion is also an important factor to avoid the damage to cochlear.

After cochleostomy to gaining access to the scala tympani had been done, the cochlear implant electrode was prepared and insert through this hole. After the tip of the electrode pass the hole, the surgeon will not able to see the tip of the electrode and need the resistance sensation to avoid the damage to the regional structure.

Todd and Naghdy [34] have developed the real-time haptic model based on real physical data and force measurements, and analysis of implant behavior during insertion. The force feedback provides the simulator user with a more realistic experience; enhancing the sense of immersion into the virtual environment than would be expected from visual representation alone. The user can see and touch the virtual environment model during manipulation. Touch sensation is a vital information channel in real-world scenarios, particularly during surgery for tool/object interactions. Haptic-rendered simulators with real-time control have increasing application in medical education. Advances in computer processing power and the development of high-fidelity force-feedback devices with specialized software enable the reproduction of realistic human models that have real-world properties.

In their model, the scala tympani was created which is the path of trajectory rather than modeled the cochlea as one chamber in other studies [35, 36]. Figure 5 shows a scala tympani in the cochlea.

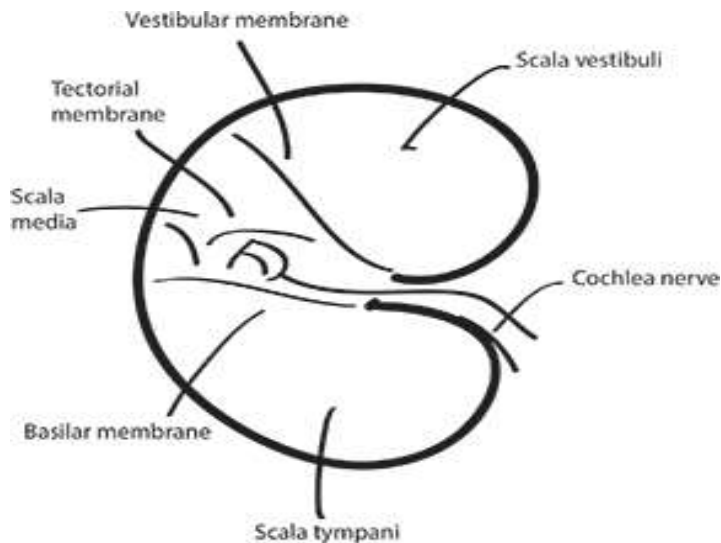


Figure 5. Cross-sectional illustration of cochlear.

The Toddd and Naghdy system design included cochlear implant insertion analysis and scala tympani parametric modeling, model optimizations and integration of features for enabling interactive, real-time insertion of a virtual implant into the model, with visual and force feedback delivered to the user during cochlear implant advancement. Upon running the simulation, the user can interact with the virtual environment using the haptic device. Force feedback is provided to the user as the surgeon performs real-time, virtual cochlear implantation into a surface description of the human scala tympani.

The result from this study found that the degree of similarity between their virtual model and Teflon model of scala tympani is moderate. The electrode still has a chance of displacements from 0 to 5.3mm, 5.9 to 9.6 mm, 11.5 to 11.8 mm and 13.1 to 16.1 mm.

They proposed the future work that includes modeling the basal membrane as a soft tissue structure, enabling surface deformations and puncturing, as well as the construction of the scala vestibuli as a secondary chamber for CI insertion.

Who Can Get the Benefit of Virtual Reality System for Cochlear Implant Surgery?

1. A child with profound hearing loss or deafness will get the most benefit from this system. As the anatomical structures of the child are still developing and do not reach the maximal growth point, the chance that the structure will be varied from the landmark that we usually encounter in the adults is high.
2. An adult with the distortion of the anatomy. The distortion usually resulted from the diseases such as chronic otitis media or cholesteatoma. The diseases will destroy or invade the surrounding structure and distort the anatomical landmark.
3. The profound or deafness patients who will undergo a cochlear implant surgery, but does not have a particular condition can also ask the surgeon to do the rehearsal for the safety reason.

4. The surgeon himself will get confidence after a rehearsal in complicated cases.
5. The trainee surgeon can practice in the virtual reality system before entering the operating room.

CONCLUSION

The virtual reality surgical training for cochlear implantation is in the development stage. An early result showed that this procedure is feasible and can enhance the safety of the patients. The implementation of this system will be happening soon after the results from clinical trials are published.

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Chapter 52

CROSS-MODAL PLASTICITY IN DEAF CHILDREN WITH VISUAL-IMPAIRMENT: ELECTROPHYSIOLOGICAL RESULTS AFTER LONG-TERM USE OF COCHLEAR IMPLANTS

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ABSTRACT

Introduction: Given the multidimensional scope of Cochlear Implants (CI), there are growing needs to provide others measures for assessing the impact of the cochlear implantation, such as brain reorganization besides clinical measures of outcome related to communicative abilities.

Objective: To assess the Cross-Modal Plasticity in deaf children with visual-impairment after CI use, through the analysis of changes of the topographic distribution the cortical response of Somatosensory Evoked Potential by stimulation of median nerve.

Methods: A case-control prospective study was carried out in a group of nine deaf children with visual-impairment. Cross-Modal Plasticity assessment was performed by testing Somatosensory Evoked Potentials (cortical response to median nerve stimulation, SEP N20) at different periods: prior to cochlear implantation and after the use of CI (after one and five years). In this chapter, we describe the results of Low-Resolution Brain

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Electromagnetic Tomography (LORETA) used for the localization of electrical neuronal sources generators of SEP N20 response in deaf children with visual-impairment.

Results: Cochlear Implants had a positive effect on lives of implanted children and their families. The study included results on topographic distribution the cortical response of SEP N20 where the visual and auditory areas are widely activated with somesthetic stimuli in deaf children with visual-impairment with 7 or more years of sensory deprivation before implantation. A significant reduction in the topography of SEP N20 was observed after five years of stimulation via CI. The analysis of the individual maps showed reduction of the over-activation found in children with 7 or more years before implantation, except for one child. These changes are related to the general development potential, possible concurrent conditions, and progression of the severity of the visual-impairment.

Conclusion: This study makes available electrophysiological evidence about Cross-Modal Plasticity in deaf children with visual-impairment after long-term use of CI. Changes in the topography of cortical response of SEP N20 could be observed in these children who receive CI, suggesting new brain reorganization of the auditory cortex when stimulated through CI. Evidences of Cross-Modal Plasticity may be an expression of how important is the somesthetic information in these subjects, probably due to the relationship with tactile language, as well as the functional interaction of auditory and somesthetic information during the auditory (re)habilitation post-CI.

Keywords. Cross-Modal Plasticity, deaf children with visual-impairment, Somatosensory Evoked Potentials, cochlear implant, low-resolution brain electromagnetic tomography, LORETA

INTRODUCTION

The severe-to-profound sensorineural hearing loss (SNHL), associated with a visual impairment that classified as deaf-blindness, is a serious health problem. It is crucial that, once identified, children with these disabilities should be properly studied and the diagnosis of their health condition be established.

Studies in the last decade have shown that the cochlear implant (CI) is an effective treatment for children who have a severe-to-profound SNHL, and do not show any benefit with modern hearing digital aids (Archbold and Mayer 2012; Gilley 2010; Wilson and Dorman 2008).

Most studies on the impact of CI have focused on clinical assessments of efficacy (hearing and speech skills, and auditory thresholds). However, these measures are only part of the effect of CI treatment. Given the multidimensional scope of CI, there are growing needs to provide others measures for assessing the impact of the cochlear implantation, such as Cross-Modal Plasticity.

Plasticity in its broadest form refers to the neurons and networks ability to change their function as a result of intrinsically or extrinsically driven factors. When cortical regions do not receive adequate sensory input, these brain regions become vulnerable to recruitment from other sensory modalities (Shiell 2014; Hauthal 2013; Lomber 2010; Finney 2001). Brain plasticity is an often overlooked yet important factor that may influence clinical outcomes in hearing impaired individuals who receive intervention via hearing aids or CI. Moreover, brain

plasticity provides the framework upon which (re)habilitation and therapy initiatives for these clinical populations could be based.

Functional Magnetic Resonance Imaging (fMRI) is the most used tool in published research on neuroplasticity in subjects with single sensory deprivation, visual or auditory (Merabet and Pascual-Leone 2010; Bavellier and Neville 2002; Sadato 2002; Finney 2001). Recent evidence suggests that deafness is associated with cortical plasticity in temporal brain regions that is correlated with CI outcome (Lee 2010, 2001). Unfortunately, research efforts in this field have been hindered by the incompatibility of most conventional neuroimaging techniques with a CI, due to electromagnetic artefacts associated with the implanted device (MRIsafety 2012). However, the electrophysiological techniques such as Evoked Potentials are particularly useful for the study of neuroplasticity (Charroó-Ruiz 2013, 2012; Eggermont 2003; Neville 1987, 1983).

The study of the topographic distribution maps of Somatosensory Evoked Potential by stimulation of median nerve (SEP N20) could reflect possible neuroplastic changes that occur at the cortical level as a result of the auditory (re)habilitation post-CI. In this case, it is expected that changes that take place in the pattern of activation of brain regions be reflected in the SEP N20 topographic maps. To study the dynamics of such reversed cross-modal plasticity, we designed a longitudinal study involving the follow-up CI receivers one and five years post auditory (re)habilitation.

Objective: To assess Cross-Modal Plasticity, specifically cortical reorganization in deaf children with visual-impairment after Cochlear Implant use, through the analysis of changes of Somatosensory Evoked Potential topographic cortical response distribution by stimulation of the median nerve.

METHODS

This was a case-control prospective study with a group of nine deaf children with visual-impairment that had received a single CI, with complete insertion of the electrodes. None of these children had surgical complications. Table 1 shows additional participant data.

Table 1. Demographic information about deaf children with visual-impairment and CI

Age at surgery (years)	9 Mean (Min 3 and Max 15), 4,46 DS
Age at evaluation –one year after CI (years)	10 Mean (Min 4 and Max 16), 4,48 DS
Age at evaluation –five years after CI (years)	14 Mean (Min 8 and Max 20), 4,46 DS
Sex	Four male Five female
Unilateral CI	Right = 5 Left = 4
Bilateral SNHL	Pre-lingual= 7 Peri-lingual= 2

The deaf children with visual-impairment had been receiving auditory (re)habilitation. The results of the auditory (re)habilitation were assessed using tests that were developed and validated internationally for such purposes by others authors (Comité Español de

Audiofonología 2005; Huarte 1996). According to the auditory skills and language development, each child was assigned to the phases of auditory (re)habilitation: (1) detection, (2) discrimination, (3) identification, (4) recognition, and (5) comprehension (Amat and Pujol 2006).

A control group of 23 healthy children, with normal hearing and vision, was selected, to create reference patterns for the evaluation of the topographic distribution maps of the SEP N20 (see Charroó-Ruiz 2012, for details about this sample).

Cross-Modal Plasticity assessment was performed by testing SEP N20 at different periods: prior cochlear implantation and after CI use (one and five years after). Recordings post-CI SEP N20 and topographic distribution maps of the cortical response were obtained with the same protocol and procedure used in pre-CI study of deaf children with visual-impairment, and the healthy children of the control group (see Charroó-Ruiz 2012, for details about stimuli and methodology used).

Grand-average SEP N20 topographic maps of deaf children with visual-impairment were obtained at 3 different moments (pre-CI, one and five years after implantation). Comparisons between one and five years after implantation studies with the pre-CI study (baseline) were carried out using the permutation test.

In this chapter, we used the Low-Resolution Brain Electromagnetic Tomography (LORETA, Pascual-Marqui 2002) to localize electric neuronal distribution of the SEP N20 in the cortex in deaf children with visual-impairment before and after CI and healthy children of the control group.

The individual maps of each deaf child with visual-impairment were compared, through visual inspection, with the average maps of the SEP N20 obtained from the control group as reference. (Charroó-Ruiz 2012) Also comparisons between the pre-CI versus post-CI results were done for each child. The progress in the auditory (re)habilitation was considered in this analysis.

Ethical issues: The institutional review board approved the study and the free informed consent. All parents signed the free informed consent form after agreeing their children to participate in the study, in accordance with local ethics committees and with the Declaration of Helsinki.

RESULTS

Figure 1 shows average maps of the topographic distribution of SEP N20 at 3 different moments (pre-CI, one and five years after implantation, up panel). It is observed extensive cross-modal reorganization of the areas corresponding to auditory and visual cortices by somatosensory stimulation in pre-CI study (baseline, first map in the up panel). The comparison between studies carried out one year after implantation versus baseline (middle panel) did not show any statistically significant difference when the permutation test was used. However, after five years of stimulation via CI an important statistically significant reduction in the topography of SEP N20 was observed, in the left temporal regions (derivation T5, low panel).

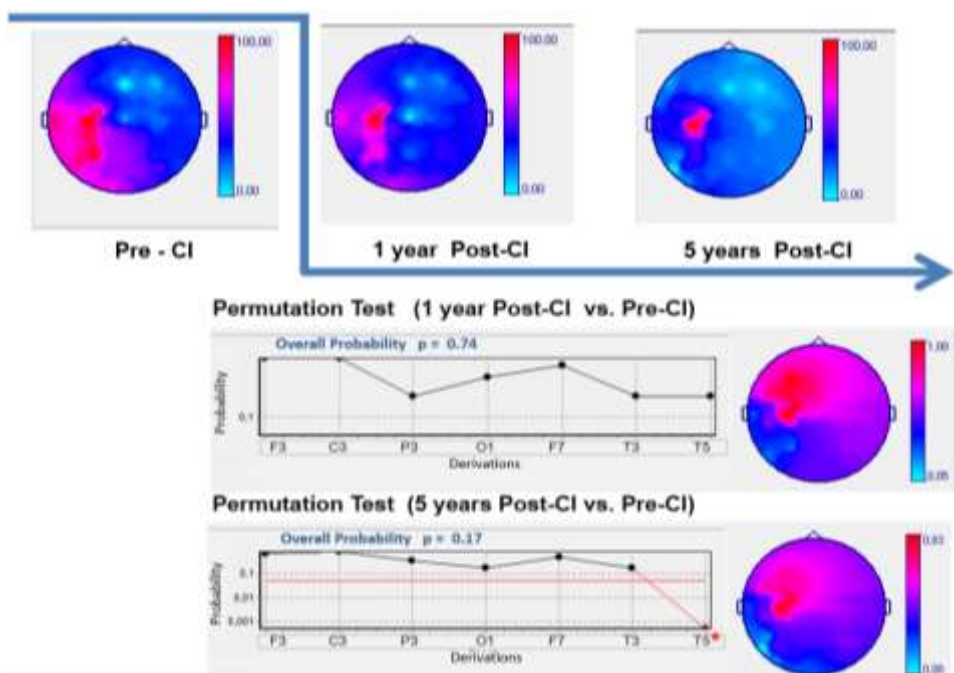


Figure 1. Grand-average SEP N20 topographic maps of deaf children with visual-impairment Pre-CI and Post-CI (up panel). Results the Permutation Test (low panel).

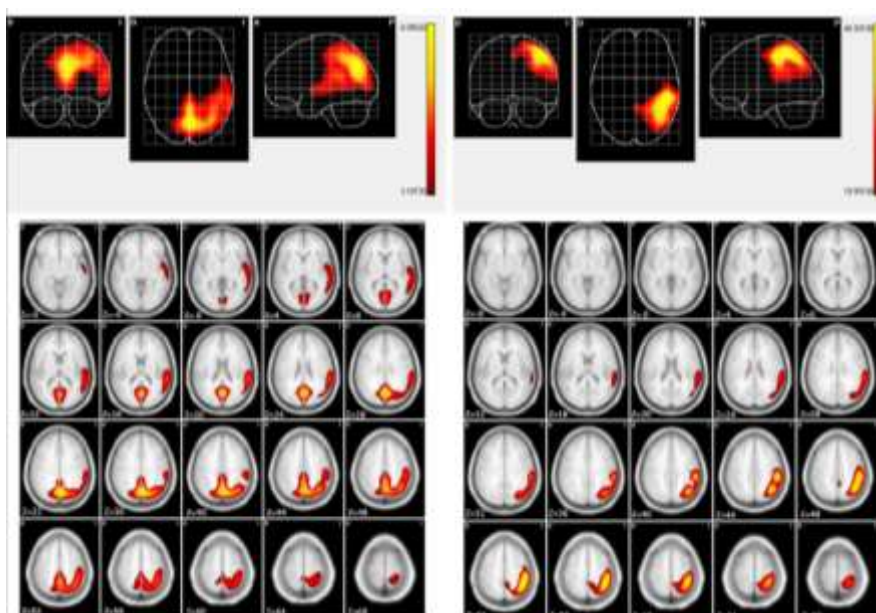


Figure 2. The anatomical distribution of the electric sources of cortical response SEP N20 Pre-CI localized by LORETA in deaf children with visual-impairment (on the left) and a healthy children (on the right). Maximum projection of the solution (up panel). The scale in the right corner ranging from red to yellow shown activation level (yellow is highest level activation). All views (low panel). Axial sections from Z=-8 to 68.

One analysis to localize the electric neuronal sources of SEP N20 by LORETA in deaf children with visual-impairment, and in healthy children, with normal hearing and vision, showed activation in different cortical regions: somatosensory, auditory and visual in children with dual sensory deprivation before CI, suggesting cross-modal recruitment of auditory and visual regions by somatosensory processing, while the somatosensory stimulation results were only significant in somatosensory cortex in healthy children. Figure 2 shows typical regions of SEP N20 obtained from electrical stimulation of the median nerve in children of both groups, and the name of the activated cortical regions are described in Table 2.

Figure 3 depicts individual maps of the response to somatosensory stimulation of deaf children with visual-impairment before CI (up panel) and five years after implantation (low panel). SEP N20 individual topographic maps show regular activation in somatosensory cortex (post-central gyrus) 5 years after CI (low panel) in each child. It is shown a reduction of the over-activation (SEP N20) found in children with 7 years or more of the deafness duration before implantation. Only one child after CI (low panel, and child 5) showed cortical activation in the primary somatosensory cortex (post-central gyrus, parietal cortex) as well as auditory and visual cortices (an over-representation of the SEP N20 more intense in comparison with baseline).

Table 2. Brain areas that showed activation with somatosensory stimulation (SEP N20) in deaf children with visual-impairment and healthy children accoring to voxel-by-voxel with Low-Resolution Brain Electromagnetic Tomography (LORETA)

Deaf children with visual-impairment				
x (mm)	y (mm)	z (mm)	Brodmann Area (s)	Anatomical Locations
-59	-29	40	2	Primary Somatosensory Cortex
-55	-23	40	3	Primary Somatosensory Cortex
-6	-54	56	5	Somatosensory Association Cortex
-6	-70	36	7	Visuo-Motor Coordination
-60	-37	16	42	Audotory Cortex
-56	-33	40	40	Supramarginalgyrus (Wernicke’s area)
-47	-63	40	39	Angular gyrus (Wernicke’s area)
-57	-10	12	22	Superior Temporal gyrus (Wernicke’s area)
-53	-12	-12	21	Middle Temporal gyrus
-12	-76	6	17	Primary Visual Cortex (V1)
-16	-70	6	18	Secondary Visual Cortex (V2)
-31	-70	26	19	Associative Visual Cortex (V3, V4, V5)
-49	-19	52	4	Primary Motor Cortex

Healthy children with normal hearing and vision

x (mm)	y (mm)	z (mm)	Brodmann Area (s)	Anatomical Locations
-46	-30	53	3	Primary Somatosensory Cortex
-46	-38	51	2	Primary Somatosensory Cortex
-32	-66	52	7	Visuo-Motor Coordination
-46	-19	50	4	Primary Motor Cortex

The Montreal Neurological Institute (MNI) coordinates are given in millimeters, and the origin is at the anterior commissure. For x, negative values represent left, and positive values represent right. For y, negative values represent posterior, and positive values represent anterior. For z, negative values represent inferior, and positive values represent superior.

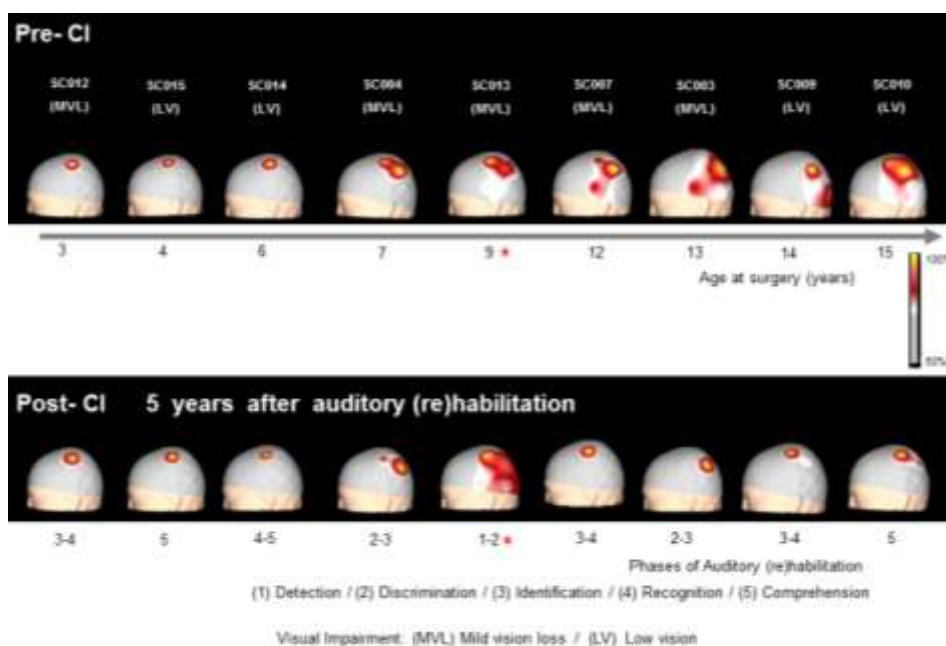


Figure 3. SEP N20 individual topographic maps of the deaf children with visual-impairment before CI, and five years after CI.

In the present study, CI treatment showed a positive effect on the lives of implanted children and their families, because communication skills and quality of life were much better after years of the auditory (re)habilitation. All these children with CI became able to attend school. Only one child remained with significantly limited communication skills, using only tactile language. Although this child were 5 years in auditory (re)habilitation, it was observed a poor progress in the transited phases of (re)habilitation (see Figure 3, low panel, and child 5). Meanwhile, the other eight implanted children reached the upper phases of the auditory (re)habilitation. Even two of them reached the comprehension phase, the last phase of the auditory (re)habilitation indicating a good use of the CI (see Figure 3, low panel, child 2 and child 9).

DISCUSSION

Our study provides new evidence of Cross-Modal Plasticity through the changes in the topographic distribution of SEP N20, in deaf children with visual-impairment after cochlear implantation. SEP N20 topographic changes were interpreted as expression of the relevance of the somesthetic information in children with dual sensory deprivation (auditory and visual). The most interesting findings were related to the duration of the deprivation, presented in children with 7 or more years of sensory deprivation before the CI. While somatosensory stimuli activates gyrus post-central in normal subjects, (Charroó-Ruíz 2012; Kakigi 1991) the activity level elicited in this region in deaf children with visual-impairment is abnormal in studies pre-CI with overall representation in auditory and visual cortices. However, these abnormal activity levels decrease with post-implantation time and tend towards the levels observed in normal subjects, provided there is no worsening of visual-impairment or other health problems, such as cognitive limitations and cerebral palsy.

Cross-Modal Plasticity has been observed in somatosensory modality in deaf subjects (Auer 2007; Caetano 2006; Leväne 2001, 1998), while, there are very few studies about the neuroplasticity in deaf-blindness (Obretenova 2010; Osaki 2006, 2004). Previous works have in common that they have studied a single adult subject with deaf-blindness, and reported cortical activation pattern to tactile stimulation, which agree with our findings.

Our study revealed that neuroplasticity after cochlear implantation involves not only auditory processing networks. Our results suggest that with deaf-blindness, the functional links between cortical regions specialized in auditory and visual processing are reallocated by somatosensory input to support tactile language processing as result of the cross-modal reorganization before CI, and this changed after auditory input from the CI.

Prospective longitudinal studies provide important information concerning the timeline of cross-modal reorganization according to duration of hearing loss, including a measure of the degree of re-organization. In addition, such studies may indicate the effect of clinical interventions, such as cochlear implantation, in reversing cross-modal reorganization, as shown in the present study. We sought to examine whether after CI new cross-modal recruitment is limited to the early stages after implantation (first year of the auditory (re)habilitation post-CI) or whether Cross-Modal Plasticity accompanies the long process of (re)habilitation with CI (5 years). These results post-CI showed that the most important and significant changes occur at long-term.

Why do not think that the less intense use of the hands to communicate after the auditory (re)habilitation post-CI may reflect changes in the topography of the SEP N20? We could speculate that the arrival of the auditory sensory input through the CI on temporal cortex in these children competes with the other modalities of sensory input that were established in these areas before the CI. The auditory sensory input “competes” with the somesthetic information that activated the temporal region in the left hemisphere previously to the implantation. This is precisely the cortical brain area where the neural basis of hearing and language are established. However, the input and processing of sensory information at the cortical level is the result of complex processes taking place, where different areas are involved in the information processing that arrive to the brain cortex.

Nowadays, there have been reported neuroplastic changes involving the activation of the temporal region in deaf children who received CI (Gilley 2008). Although less studied in

deaf-blindness it has been also reported that the auditory stimulus presentation has been able to activate the temporal region, in this case using Positron Emission Tomography (Osaki 2006).

A central issue in the field of pediatric CI is the optimal age for implant and predicting cochlear implant outcome from brain organization in the deaf (Giraud 2007; Geers 2006; Nicholas and Geers 2006; Sharma 2002). The findings support the assertion that early cochlear implantation yields the best cochlear implant performance, which is likely associated with higher degree of synaptic plasticity within the auditory system. Positive changes in speech comprehension and production with time and training after implantation should be unsurprising, given the large literature on plasticity within the auditory system in relation to language learning and after hearing loss (Eggermont 2008). A common theme among these studies is that the auditory cortex can be rapidly, profoundly, and persistently reorganized by changes in sensory inputs and practice with speech production and comprehension. The perisylvian cortex of the temporal lobe contains Broca's and Wernicke's areas, and has been found to have an extended maturational period, continuing through at least 14 years of age in relation to speech perception and 30 years of age for gray matter thickness (Ross 2011; Sowell 2004). Although there is undoubtedly a critical period during early childhood development for language learning, recently Schlegel et al. (2012) have used diffusion tensor imaging to examine changes to white matter in adults learning a second language. Over a 9 month period of an intensive course in modern Chinese, imaging in students indicated that myelination increased in cortical language centers, and the degree of changes for each subject correlated with their proficiency with the new language. Importantly, the cortex seems to remain functional and plastic after sensory deprivation and despite the reductions in potential Cross-Modal Plasticity, cochlear implant use seems able to recover some degree of functionality in central auditory regions (Ross 2011). Our findings reveal that individuals implanted at a late age also benefit from implantation indicative of persistent capacity for neuroplasticity within the auditory cortex with a positive effect on the lives of implanted children and their families.

In deaf children the use of a CI allows a recovery of the auditory function, which will probably counteract the cortical cross-modal reorganization induced by hearing loss. Although the data above presented are a case study, they may add to the growing body of evidence that cross-modal reorganization does occur in some CI recipients, and that cross-modal recruitment may be related with outcomes.

The new cross-modal reorganization was observed consistently in each child (with 7 or more years of sensory deprivation before the CI) across all of the cortical regions examined post-CI. The restoration of audition by CI has improved the communication skills (listening, and spoken language, or a combination of tactile language and auditory oral) in deaf children with visual-impairment, albeit with varied results. Only a child with cerebral palsy and cognitive retardation (see Figure 3, low panel, and child 5) showed very poor auditory and phonological abilities (tactile language).

Several causes may be influencing the change of the topographic distribution of the SEP N20 post-CI in only one deaf-blind child showing an extensive topographic distribution of SEP N20 compared with the pre-CI study. This finding could be considered as the result, among other causes, of the progression of visual-impairment in this child. We have reported that, changes in the topographic distribution of the SEP N20 by right median nerve stimulation pre-CI in deaf children with visual-impairment seem to be related to the early-

onset of dual sensory deprivation (deaf-blindness) and severity of the visual- impairment (Charroó-Ruíz 2012). This child suffers of *Retinitis Pigmentosa*. The visual test-retest by one of our co-authors showed a progression of visual loss after 5 years of the implantation. Moreover, in the results of the auditory (re)habilitation of this child it is important to note that due to illness and irregularities with the (re)habilitation in her health area, this patient could not receive continuous and intensive auditory therapy, such as the other studied children; therefore, she did not perform the auditory (re)habilitation schedule proposal according to the Cuban Cochlear Implant Program. These reasons could explain the poor and slow progress observed in this child, who only reached the (re)habilitation phases of detection/discrimination, and continues using the tactile language as a primary mode of communication at home and at school. Some authors describe that deaf children with SNHL who receive a CI require at least 4 years of intensive auditory (re)habilitation to achieve maximum benefit with CI (Archbold and O'Donoghue 2009; Bond 2009). In addition, this child that showed over-representation of the SEP N20 post-CI has an additional disability (cerebral palsy and cognitive retardation) which should be considered as another factor that may influence on the poor outcome.

Cognitive limitations and retarded development are found in a significant number of cochlear implantation users (Lesinski 1995). Children with cognitive retardation required more time and experience with their CI to achieve sentence comprehension and expressive language. Overall, they showed less favorable speech development than children without cognitive limitations. Lee et al. (2010) showed that speech perception and production were negatively correlated with the degree of mental retardation. On the other hand, to date, relatively little information is available on children with cerebral palsy, but in general, there is considerable variability in performance outcomes, that correlated negatively with the severity of additional handicaps present.

Clinical reports indicate that additional handicaps are found in more than 40% of hearing-impairment children (Nikolopoulos 2006). The most frequent handicaps are retardation in motor and mental development, and visual- impairment among others. Each individual case must be examined to address the potential prognosis and, even more importantly, the specific needs and capacity of the child to undergo and derive benefit from the (re)habilitation process.

Children with dual sensory deprivation comprise a very heterogeneous group in terms of the outcomes displayed post-CI. It must be at least assumed that this disease pattern may have an unfavorable influence on the development of speech and hearing skills. Basically, in treating patients with multiple handicaps, it is important to consider not only the individual constellation of the separate symptoms and comorbidities, but also to define expectations from cochlear implantation. Overall, it appears difficult to generally make valid predictions; nonetheless, the study by Nikolopoulos et al. (2008) showed that long-term results for patients with additional handicaps depend essentially on the number of additional handicaps. Our results are in agreement with these criteria. For children considered to be complex cases, the aim of CI treatment is not necessarily the oral communication capabilities. The aim may be recognition of the parents' voices or enable awareness, contact, and a sense of security with their environment, which concurrently has a positive influence on the functional capabilities in areas of social or emotional behavior. It is, however, enormously important that the (re)habilitation process after CI appropriately addresses the needs of these complex children.

There are few published studies in children with dual sensory deprivation (Filipo 2004; El-Kashlam 2001; Saeed 1998). In general, publications are limited to the description of the auditory progression after the CI, and we did not find others studies about electrophysiology assessment and neuroplasticity results in these children. It is argued that children with dual sensory deprivation, generally, have poor progress in the production of words or sentences (Dammeyer 2009). However, the improvement that these children can have from the point of view of family interaction, with their environment, in their level of attention and emotional state justifies any effort to works in the benefit of these children through CI programs.

Overall, the electrophysiological and behavioral results that we describe are strongly indicative of cross-modal reorganization in deaf children with visual-impairment after CI, and at the same time, it is evident the positive benefit of auditory (re)habilitation for these children. These are new findings that add to the previous reports about Cross-Modal Plasticity that have been obtained in our laboratory in children with deaf-blindness or deafness (Charrooó-Ruíz 2014, 2013, 2012).

It should be noted that deaf-blindness is a condition in which each subject behaves with marked individuality, especially, when dual sensory deprivation begins at birth, where the two main sensory systems to acquire information from the environment and achieve a normal development are affected. In children with dual sensory deprivation occurs a very peculiar adaptive brain re-organization, therefore the Central Nervous System matures in a different way. It is difficult to form homogeneous groups of children with deaf-blindness to increase samples. In addition, nowadays there are few subjects with dual sensory deprivation that could be candidates for CI, and definitive candidacy criteria in patients with multiple disabilities and cognitive impairment do not exist (Cosetti and Waltzman 2011). In any case, deaf-blindness is an interesting model for future research to help get into the particularities that occur in auditory cortical processing after of the cochlear implantation and learning of the oral language.

Lastly, importantly and perhaps surprisingly, our study offers evidence of Cross-Modal Plasticity in children with long-term sensory deprivation before CI. Understanding Cross-Modal Plasticity in the context of dual sensory deprivation, and the potential for reversion of these changes following intervention, may be vital in directing intervention and (re)habilitation options for clinical populations with hearing loss, especially in complex cases with other handicaps. As the criteria for cochlear implantation in children are expanding, clinical evidence of Cross-Modal Plasticity may play a critical role in determining whether implantation may be beneficial in non typical cases of pediatric deafness. However, to date most research shows the efficacy of cochlear implantation assessing speech perception abilities and quality of life.

In summary: This study makes available electrophysiological evidence about Cross-Modal Plasticity in deaf children with long-term visual-impairment before CI. The study included results about topographic distribution of SEP N20 where the visual and auditory areas are widely activated with somesthetic stimuli in deaf children with visual-impairment with 7 or more years of sensory deprivation before implantation. Changes in the topography of cortical response of SEP N20 can be observed in these children who receive CI, suggesting new reorganization of the auditory cortex when stimulated through CI. These changes are related to the general development potential, possible concurrent conditions, and progression of the severity of the visual-impairment. Evidences of Cross-Modal Plasticity may be an expression of how important is the somesthetic information in these subjects, probably due to

the relationship with tactile language, as well as the functional interaction of auditory and somesthetic information during the auditory (re)habilitation post-CI. Nontraditional measures such as the topographic distribution of SEP N20 could be useful in assessing the neuroplastic changes in deaf children with visual-impairment.

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Chapter 53

ANATOMY AND PHYSIOLOGY OF THE PERIPHERAL AND CENTRAL AUDITORY SYSTEM

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ABSTRACT

The auditory system is responsible for the hearing sense and it consists of the peripheral auditory system (outer, middle and inner ear) and of the central auditory system (vestibular and cochlear nuclei, auditory and vestibular pathways and vestibular and auditory cortices). The outer ear comprises the auricle and the auditory canal and its function is to guide air pressure waves to the middle ear. The middle ear consists of the tympanic membrane, connected to the inner ear by three ossicles (malleus, incus and stapes), which vibrations allow the transmission of originally airborne sound waves to the perilymph of the inner ear. The middle ear provides a pressure gain as well as enhanced quality of the sound waves transmitted to the inner ear and protects it from high pressure levels produced by loud sounds. The stapes footplate of the middle ear connects to the oval window of the cochlea, an inner ear spiral-shaped bony canal. The stapes of the middle ear connects to the oval window in the cochlea. The vibrations of a flexible membrane (basilar membrane) on which sensory cells (hair cells) reside are responsible for the transduction of the sound waves into electrical impulses.

The vestibulocochlear nerve (CN VIII) transmits both hearing and balance information from the inner ear to the brain. The vestibular (balance) and cochlear (hearing) components of the vestibulocochlear nerve target different nuclei. The vestibular component reaches the vestibular nuclei in the pons and medulla oblongata. The cochlear component instead reaches the ventral and dorsal cochlear nuclei, located laterally at the junction between the pons and medulla, in close proximity to the inferior cerebellar peduncle. CN VIII emerges from the brainstem at the cerebellopontine angle and exits the posterior cranial fossa of the neurocranium through the internal acoustic meatus of the temporal bone. Here the vestibulocochlear nerve splits, thus forming the

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vestibular nerve and the cochlear nerve. The vestibular nerve innervates the vestibular system of the inner ear, which is responsible for detecting balance. The cochlear nerve travels to the cochlea, forming the spiral ganglia of Corti, involved in the sense of hearing.

The hearing pathway originates in the cochlear nuclei which receive first-order auditory input from the organ of Corti in the cochlea. The second neuron of this pathway is located in the superior olivary nuclei of the pons where the majority of the auditory fibers synapse, crossing the midline. The fibers ascend, forming the lateral lemnisc and proceed towards the inferior colliculus in the mesencephalus. The last relay, prior to the primary auditory cortex, occurs in the medial geniculate body of the thalamus. A tonotopic organization is evident throughout the hearing pathway, from cochlea to auditory cortices.

In the balance pathway, neurons synapsing on the hair cells of maculae and cristae ampullares of the semicircular canals converge in the vestibular ganglion. The sensory fibers originating from here join the sensory fibers from the cochlear ganglion to form the vestibulocochlear nerve and terminate in the vestibular nuclei of the pons and medulla. The axons originated in these nuclei reach different areas of Central Nervous System (CNS), such as the spinal cord, the cerebral cortex, the cerebellum and the nuclei controlling extrinsic eyes muscles. The vestibular nuclei also receive input from proprioceptive neurons, as well as the visual system.

INTRODUCTION

1. Anatomical Bases of Hearing: An Overview

In this paragraph, we describe briefly the main anatomical structures involved in hearing, i.e., the ear, the vestibulocochlear nerve, the cochlear nuclei and the auditory cortex.

1.1. The Ear

From an anatomical point of view, the ear consists in three parts; the external, the middle and the internal ear. In the next paragraph, the morphology of each part will be briefly summarized.

External Ear

The external ear includes the auricle (pinna) and the external auditory canal (meatus). The *auricle* is composed of a thin plate of elastic cartilage, covered by a layer of skin. It is attached in place by ligaments, and has two groups of muscles, extrinsic and intrinsic ones. There is a deep depression (concha) that leads into the external auditory meatus and is covered by two small protrusions: the tragus, in front, and the antitragus, behind. The funnel-like curves of the auricle collect sound waves and direct them toward the middle ear.

The *external auditory meatus* is a slightly curved canal, about 2.5 cm in length, that extends from the floor of the concha to the tympanic membrane. The meatus contains two types of glands: sebaceous glands and ceruminous glands (modified sweat glands that secrete cerumen).

Between the external and the middle ear there is the *tympanic membrane*. It is a membranous structure located on the medial part of the auditory meatus. The tympanic membrane is comprised of three layers of tissue: an outer cutaneous layer, a fibrous middle layer, and a layer of mucous membrane on its innermost surface. The membrane is held in place by a thick ring of cartilage. It has the capacity to vibrate and to receive sound waves that are amplified to an appropriate magnitude. The membrane vibrates as the sound waves strike it, and transmits the vibrations towards the small bones of the middle ear.

Middle Ear

The middle ear, or tympanic cavity, is connected to the epitympanic recess, the antrum and the cells within the mastoid portion of the temporal bone. Medially, the auditory (or Eustachian) tube links the tympanic cavity with the nasopharynx. The tympanic cavity is an air-filled space, covered by a columnar epithelium, that contains 3 tiny bones (known as *ossicles*), called the malleus (hammer), incus and stapes (stirrup). Sound waves that reach the tympanic membrane cause it to vibrate. This vibration is then transmitted to the ossicles, which amplify the sound and pass the vibration to the oval window (a thin membrane between the middle and the inner ear). Hammer and stirrup movements are limited by two small muscles, the tensor tympani and the stapedius, respectively.

The Inner Ear

The inner ear consists of 1) the otic labyrinth (membranous labyrinth), 2) the periotic labyrinth (osseous labyrinth), and 3) the otic capsule (part of the petrous portion of the temporal bone which surrounds the internal ear).

The *otic labyrinth* is a closed system of endolymph-filled ducts and sacs contained within the inner ear. It has the same general shape as the osseous labyrinth and consists of structures surrounded by perilymph.

In particular, it includes the cochlea, which is involved in hearing, and the vestibular system (consisting of three semicircular canals, as well as a saccule and an utricle), which is responsible for maintaining balance. The cochlea is filled with fluid and contains the organ of Corti — a structure that contains thousands of specialized sensory hair cells with projections called cilia. The vibrations transmitted from the middle ear produce tiny waves which make the cilia vibrate. The hair cells then convert these vibrations into nerve impulses, or signals, which are sent to the brain via the auditory nerve.

The semicircular canals also contain fluid and hair cells, but these hair cells are responsible for detecting movement rather than sound. When you move your head, the fluid within the semicircular canals (which are oriented vertically at right angles to each other) also moves. This fluid motion is detected by the hair cells, which send nerve impulses about the position of the head and body to the brain to allow maintaining the balance.

The utricle and the saccule work in a similar way to the semicircular canals, providing information on the body position in relation to gravity, allowing postural adjustments as required.

The *periotic labyrinth* consists in the vestibule, the periotic semicircular canals, the scala vestibule and the scala tympani. The vestibule is the largest portion of the periotic labyrinth. It surrounds the utriculus and the sacculus. The periotic semicircular canals surround the otic semicircular ducts. They contain a great amount of periotic trabecular tissue. The scala vestibule or vestibular duct is a perilymph-filled cavity inside the cochlea of the inner ear that

conducts sound vibrations to the cochlear duct. It is separated from the cochlear duct by Reissner's membrane and extends from the vestibule of the ear to the helicotrema, where it joins the tympanic duct.

The tympanic duct or scala tympani is one of the perilymph-filled cavities separated from the cochlear duct by the basilar membrane, and it extends from the round window to the helicotrema, where it continues as the vestibular duct.

The purpose of the perilymph-filled tympanic duct and vestibular duct is to transduce the movement of air that permits to the tympanic membrane and the ossicles to vibrate, into a movement of the liquid and of the basilar membrane. The latter stimulates the organ of Corti inside the cochlear duct, composed of hair cells attached to the basilar membrane and their stereocilia embedded in the tectorial membrane. Indeed, the organ of Corti is located in the scala media of the cochlea, between the vestibular duct and the tympanic duct and is composed of mechanosensory cells, known as hair cells. These cells lie on the basilar membrane of the organ of Corti and are organized in three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs). These hair cells are supported by Deiters' cells, also called phalangeal cells. Above them is the tectorial membrane which moves in response to pressure variations in the fluid-filled tympanic and vestibular canals. The movement of the basilar membrane in relation to the tectorial membrane causes the stereocilia to bend. They then depolarize and send impulses to the brain via the cochlear nerve. This produces the sensation of sound.

The *otic capsule* is the portion of the petrous part on the temporal bone which surrounds the internal ear, derived from the embryotic mesenchyme which surrounded the early otic vesicle. A part of this mesenchymal tissue passes through the precartilaginous and cartilaginous stages prior to ossification. Therefore, the bony otic capsule is known as cartilage bone.

1.2. The Vestibulocochlear Nerve

The vestibulocochlear nerve (CN VIII) transmits both hearing and balance information from the inner ear to the brain. It consists mostly of bipolar neurons and forms two branches: the cochlear nerve and the vestibular nerve.

The vestibulocochlear nerve reaches the middle portion of the brainstem called the pons (which also contains fibers leading to the cerebellum). It runs between the base of the pons (and medulla oblongata, the lower portion of the brainstem) in the cerebellopontine angle. The vestibulocochlear nerve is accompanied by the labyrinthine artery, which usually branches off from the anterior inferior cerebellar artery (AICA) and then continues along the VIII nerve through the internal acoustic meatus to the internal ear.

The cochlear nerve, responsible of hearing, travels away from the cochlea of the inner ear where it starts as the spiral ganglion of the organ of Corti. The inner hair cells of the organ of Corti are responsible for the activation of afferent receptors in response to pressure waves reaching the basilar membrane through sound transduction.

The vestibular nerve originates from the vestibular system of the inner ear. The vestibular ganglion (Scarpa's ganglion) extends processes to five sensory organs. Three of these are the cristae located in the ampullae of the semicircular canals. Hair cells of the cristae activate afferent receptors in response to rotational acceleration. The other two sensory organs are the

maculae of the saccule and the utricle. Hair cells of the maculae in the utricle activate afferent receptors in response to linear acceleration, while hair cells of the maculae in the saccule respond to vertically directed linear force.

CN VIII emerges from the brainstem at the cerebellopontine angle and exits the posterior cranial fossa of the neurocranium through the internal acoustic meatus of the temporal bone. Here the vestibulocochlear nerve splits, thus forming the vestibular nerve and the cochlear nerve.

1.3 The Cochlear Nuclei

The vestibular (balance) and cochlear (hearing) components of the vestibulocochlear nerve target different nuclei. The vestibular component reaches the vestibular nuclei in the pons and medulla oblongata. The cochlear component instead reaches the ventral and dorsal cochlear nuclei, located laterally at the junction between the pons and medulla, near the inferior cerebellar peduncle.

The hearing pathway originates in the cochlear nuclei which receive first-order auditory input from the organ of Corti in the cochlea. The second neuron of this pathway is located in the superior olivary nuclei of the pons where the majority of the auditory fibers synapse, crossing the midline. The fibers ascend, forming the lateral lemnisc, and proceed towards the inferior colliculus in the mesencephalus. The last relay, prior to the primary auditory cortex, occurs in the medial geniculate body of the thalamus.

In the balance pathway, neurons synapsing on the hair cells of the maculae and cristae ampullares of the semicircular canals converge in the vestibular ganglion. The sensory fibers originating here join the sensory fibers from the cochlear ganglion to form the vestibulocochlear nerve, and terminate in the vestibular nuclei of the pons and the medulla. The axons originated in these nuclei reach different areas of the Central Nervous System (CNS), spinal cord, the cerebellum, the nuclei controlling extrinsic eyes muscles, thalamus, and the cerebral cortex.

1.4. The Auditory Cortex

The human auditory cortex is the part of the temporal lobe that processes auditory information.

It is located bilaterally, at the upper sides of the temporal lobes, on the superior temporal plane, within the lateral fissure and comprises parts of Heschl's gyrus and the superior temporal gyrus.

The auditory cortex was previously subdivided into primary and secondary projection areas and further association areas. The primary auditory cortex (AI) is situated in the posterior third of the superior temporal gyrus (also known as Brodmann area 41), next to Wernicke's area. The secondary auditory cortex (AII) is located more rostrally in the temporal lobe and contains Brodmann area 42. The modern divisions of the auditory cortex are the core (which includes AI), the belt, and the parabelt. The belt is the area immediately surrounding the core; the parabelt is adjacent to the lateral side of the belt. These latest areas help to integrate hearing with other sensory systems.

Studies indicate that auditory fields of the primary auditory cortex (AI) receive ascending input from the auditory thalamus, and point-to-point input from the ventral division of the medial geniculate complex; thus, it contains a precise tonotopic map. The primary auditory cortex (AI) has a topographical map of the cochlea.

Neurons in the auditory cortex are organized according to the frequency of sound to which they respond best. Neurons at one end of the auditory cortex respond best to low frequencies; neurons at the other respond best to high frequencies.

Studies have revealed the presence of six cell layers. The pyramidal cells correspond to 85% of AI. The remaining 15% are multipolar or stellate cells. Inverted stellate cells also exist (Martinotti cells), as well as cells with candelabra-shaped dendritic configurations. Most ascending fibers originate in synapse with the pyramidal cells of layer IV, but this is not always the case. However, these contacts represent only 20% of the excitatory fibers that project to cortical neurons: the other 80% comes from other neurons in the ipsilateral cortex.

The primary auditory cortex is subject to modulation by numerous neurotransmitters, including norepinephrine, which has been shown to decrease cellular excitability in all layers of the temporal cortex. Alpha-1 adrenergic receptor activation, by norepinephrine, decreases glutamatergic excitatory postsynaptic potentials at AMPA receptors.

2. PHYSIOLOGY OF THE AUDITORY SYSTEM

The auditory system detects sounds and uses acoustic cues to both identify them and locate their origin in the environment. The perceptual phenomenon called *sound* is produced in the brain by stimulating the ear with periodic longitudinal waves of alternating low and high pressure (rarefactions and compressions, respectively). These waves propagate at different speed depending on the properties of the elastic medium through which they travel (330 - 340 m/s through air). The absolute intensity of sound, measured in pascals (Pa), is related to the amplitude of the longitudinal wave; however, the intensity of audible sounds is usually measured in decibel sound pressure level (dB SPL): this logarithmic scale relates the absolute sound intensity (P_T) to a 20 μ Pa reference pressure (P_{ref}), roughly corresponding to the average human threshold at 2000 Hz. Due to its logarithmic nature, in this scale intensities of sounds are compressed, in such a way that a tenfold increase in absolute sound intensity just corresponds to a 20 dB SPL increase.

$$\text{dB SPL} = 10 \times \log_{10} \frac{(P_T)^2}{(P_{ref})^2} = 20 \times \log_{10} \frac{P_T}{P_{ref}}$$

Sounds with amplitudes from 0 to 120 dB SPL can be comfortably heard, whereas higher sound pressure levels cause pain and can damage the ear. Acoustic waves have typically an amplitude of about 60 dB in a normal conversation.

The subjective experience of tonal discrimination (*pitch*) of a sound depends on wave frequency, measured in hertz (Hz, waves per second). Humans can hear sounds in the frequency interval from ~20 to 20,000 Hz; perception of speech encompasses frequencies between 60 and 12,000 Hz.

On the basis of both temporal pattern and regularity of acoustic waves we can distinguish pure tones (characterized by a single frequency), sounds (characterized by a perceived fundamental frequency, or *pitch*, and overtones) or noises, with no recognizable periodic elements.

Sounds characterized by the same SPL but different frequencies are not perceived as equally loud; these differences in perception are accounted for by the phon scale, developed by adjusting the intensities of test tones to be equal in loudness to reference tones of 1000 Hz (normal hearing threshold is ~4 phon, whereas discomfort and pain are perceived at 110 and 130 phon, respectively).

2.1 Outer and Middle Ear Actions: Funneling and Conduction of Sound

The auditory system is specialized to discriminate frequency, amplitude, and direction of acoustic waves, as well as to interpret temporal patterns of sound amplitude and frequency of words and music.

In the outer ear the pinna and the tragus together funnel sound waves into the external auditory canal, focusing sound waves on the tympanic membrane (or eardrum). Depending on the angle of incidence, the same sound is reflected differently off the pinna and tragus: on this basis, these structures are able to emphasize some sound frequencies over others, inducing peaks and *notches* in the sound spectrum. The positions of peaks and notches depend on (and provide information about) location of the sound source, even when using only one ear (monaural sound localization); such information is important for localizing sounds in the vertical plane (elevation). Then, each heard sound is a combination of both a direct component and a reflected one (by pinna and tragus), and causes the tympanic membrane to vibrate.

The middle ear, represented by the air-filled chamber between the tympanic membrane on one side and the oval window on the other, ensures efficient transmission of sound from air into the fluid-filled inner ear, by transferring vibrations of the tympanic membrane to the oval window through a chain of three delicate bones called ossicles: the malleus (or hammer), incus (anvil), and stapes (stirrup). Since water is highly incompressible and dense, it has very higher acoustic impedance (defined as the ratio of sound pressure to volume velocity) than air (about 10,000 times higher) and sound traveling directly from air to water has insufficient pressure to move the dense water molecules: then, transferring sound vibrations from air to cochlear fluid needs an *impedance-matching device* that saves most of sound's energy, which would be otherwise largely (>97%) reflected back to air when encountering a watery medium exerting a stronger opposition to movement brought about by a pressure wave. Impedance matching, and successful transferring of most energy to inner ear fluids, is obtained through amplification (gain of about 25 to 30 dB in the middle frequencies), due to both a larger area of eardrum than the footplate of the stapes (~ 20:1 ratio) and, to a lesser extent, a lever action exerted by malleus and incus, increasing the pressure applied to the footplate (the combined action of eardrum/footplate ratio and ossicles lever causes a ~ 55 times pressure increase over the oval window). For lower and higher frequencies, however, more energy is lost. Equalization of air pressure on opposite sides of the tympanic membrane is realized through the eustachian tube, which connects the middle ear to the nasopharynx.

2.2 Inner Ear Function: Transduction of Sound

Movements of the stapes against the oval window create traveling pressure waves within the cochlear fluids. Each movement of the oval window induce changes in pressure of scala vestibuli (inward = increase, outward = decrease) and opposite movements of round window and changes in scala tympani. The different pressure between scala tympani and scala vestibuli causes the basilar membrane (and the organ of Corti) to bow upward (when pressure in scala vestibuli > scala tympani) or downward.

The contraction of muscles of the middle ear, tensor tympani (inserted onto the malleus) and the stapedius (inserted onto the stapes), reflexively activated by high sound levels, dampen the transfer of sound to the inner ear by controlling the stiffness of the ossicular chain, in this way exerting a protective action and a suppression of self-produced sounds (e.g., voice, chewing).

Sound frequency and amplitude are encoded in the cochlea and further analyzed in the CNS. In fact, the cochlea performs as a spectral analyzer, evaluating complex sounds according to their pure tonal components, in such a way that each pure tone stimulates a specific region; in fact, different regions of the basilar membrane are tuned to particular frequencies. The *frequency* of the sound determines which region of basilar membrane vibrates most along the cochlea, high frequencies generating maximal vibrations in the basal region, whereas lower frequencies generate their maximal amplitudes near the cochlear apex, thus determining which hair cells of the organ of Corti are stimulated. In the auditory system, a *place coding* is based on this selectivity. Such low-apical to high-basal gradient of resonance is underlain by mechanical characteristics (stiffness and taper) of the basilar membrane. In fact, whereas the cochlea tapers from base to apex, the basilar membrane tapers in the opposite direction, being wider at the apex; moreover, the narrow basal end is stiffer (~100 times) than the apical end. However, the intrinsic frequency selectivity afforded by basilar membrane tuning is not great enough to account for the very selective responses observed in hair cells and auditory nerve fibers; in fact, active mechanisms are necessary to achieve this high frequency selectivity (see below).

2.3 Hair Cells Functions

The vibration of basilar membrane is transduced by hair cells of organ of Corti, mechanoreceptors specialized to detect very small movement along one particular axis, located at the junction between endolymph and perilymph; these polarized epithelial cells are characterized by an apical end specialized to transduce mechanical energy into receptor currents, whereas the basal end is in contact with perilymph and synaptically drives the activity of primary afferent neurons of the acoustic nerve (Hudspeth and Corey, 1977). In the apical end, the stereovilli of *inner* hair cells float freely in the endolymph, whereas the stereovilli of the *outer* hair cells project into the cantilevered tectorial membrane, free to tilt up and down since it is attached only along one edge. Inner hair cells transduce mechanical energy of sound into electrical energy, whereas the active movements of outer hair cells modulate the amplification of the signal. Due to a K^+ gradient, auditory endolymph has a positive voltage relative to the perilymph (+80 to +90 mV), being this endocochlear potential

the driving force for sensory transduction in both inner and outer auditory hair cells. The composition of endolymph increases the K^+ transduction current flowing from endolymph into the hair cells, due to both the concentration gradient and the large electrical gradient. Once a sound stimulates the cochlea, K^+ flows into the hair cells with little energy expenditure by the hair cells, as K^+ is flowing down its electrochemical gradient; that is why hair cells do not require a high blood flow, that would bring noise and interfere with sound reception.

In hair cells, receptor potentials are evoked by mechanically gated ion channels: in fact, specialized elastic filaments called *tip links* (or *gating springs*) are present at the tips of stereocilia, mechanically attaching (like a spring) the top of each stereocilium to the upper side of the adjacent taller one, in line with the axis of maximal bundle sensitivity (Brownell et al, 1985; Pickles et al, 1984). Destruction of the tip links by enzymatic (elastase) or chemical (calcium chelators) treatments can abolish mechanical transduction. Deflection of stereocilia in the excitatory direction stretches the tip links and increases their tension, in this way pulling on the channel gate and increasing the probability of channel opening. Deflection in the opposite direction release the tip link and let the channels close. Maximum compliance of stereocilia bundle occurs when roughly half the transduction channels are open. As a consequence of direct gating of transduction channels, hair cell transduction occurs much faster than in other sensory modalities: the delay between bundle deflection and the onset of receptor current is about 10 ms at 37°C, being such speed essential in order to detect sound frequencies in auditory range of Humans.

When the hair bundle is in resting position a standing inward cations (mainly potassium and small amount of calcium) current flows through 15-20% of mechanically activated channels, located near the tips of the stereocilia (one or two channels per stereocilium), and this inward positive current tends to depolarize the hair cells. Maximal transducer conductance changes up to about 10 nS have been observed. The proportion of open channels, and consequently the inward current, are increased when the hair bundle is displaced toward the tallest stereocilium; the current flowing across the basolateral membrane depolarizes the membrane, activating some voltage-dependent conductances. On the contrary, movement of the stereocilia bundle away from the tallest stereocilium hyperpolarizes the basolateral membrane of hair cells by reducing the inward current: remarkably, displacements in depolarizing direction produce larger responses than equal deflections in the opposite direction, describing a sigmoidal displacement–response function, shifted from its midpoint; because of such relationship, changes in membrane potential due to acoustic stimuli inducing symmetrical sinusoidal deflections of the bundle will produce both sinusoidal (AC) and superimposed depolarizing steady-state (DC) changes, the system being saturated by 300 nm deflections.

It must be noted that, whereas receptor currents are induced without attenuation across frequency, receptor potentials are susceptible to filter characteristics of the basolateral membrane depending on the time constant, ranging from sub- millisecond to a few milliseconds duration at the resting potential; this passive property lets the membrane act as a low-pass filter with a dynamic cutoff frequency ranging from tens of hertz to about 1 kHz. Furthermore, receptor potentials may activate voltage-dependent channels in the basolateral membrane, in this way modifying the resistive component of the time constant. Moreover, the capacitance of the basolateral membrane is also highly voltage dependent in outer hair cells:

in these cells the membrane filter could therefore be influenced by changes in both resistive and capacitive components. Due to the filtering of the basolateral membrane, the AC component of receptor potential is halved for every octave increase in frequency above the cutoff, becoming negligible at very high frequencies; on the contrary, the DC component of receptor potential is not affected (this effect is called *rectification*). A fundamental difference is observed between main responses to electrical changes in inner versus outer hair cells: inner cells modify the amount of neurotransmitter released at the level of synapses with afferent neurons, outer cells change their length and thereby amplify the movement of the basilar membrane.

In the inner hair cells synapse, the release of neurotransmitter depends on membrane receptor potential. In resting position the depolarizing inward cation current induces a basal neurotransmitter release: further depolarization increases the number of released vesicles, whereas hyperpolarization decreases it.

On the other side, outer hair cells express an integral membrane motor protein termed prestin along their lateral wall and are able to respond to electrical stimulation by altering their length in a voltage dependent manner: depolarization shortens the cell, whereas hyperpolarization induces elongations (Liberman et al, 2002; Zheng et al, 2000). When basilar membrane moves upward, a shear force between stereocilia of outer hair cells and the tectorial membrane develops, forcing hair bundles to tilt toward longer stereocilia: this movement opens transduction channels in outer hair cells, through which K^+ flows inward, further depolarizing the cells (the voltage change is termed receptor potential). This process is called mechanical to electrical transduction, and the consequent depolarization contracts the motor protein prestin, a member of the SLC26 family, which outer cells express at very high levels: the contraction of reciprocally linked prestin molecules shorten the outer cells (the process is called electromotility or electrical to mechanical transduction). This voltage dependent mechanical response, only limited to outer hair cells, is not evoked by activation of voltage-dependent ionic conductance.

On the contrary, *downward* movements of the basilar membrane induce hyperpolarization of outer cells and their elongation. This motor activity is restricted to the lateral membrane of the outer cell. Length changes up to 5% are observed: they are not dependent on ATP, microtubule or actin systems, extracellular Ca^{2+} , or changes in cell volume. The maximum sensitivity of the response is about 30 nm/mV, observed at a depolarized voltage with respect to the resting potential of the cell. This motor activity is maintained and modulated through the intervention of a stretch-activated chloride conductance, and intracellular chloride is required for the activity of the voltage sensor. *In vivo*, the motor action of outer hair cells is probably responsible for otoacoustic emissions.

Remarkably, the voltage-dependent mechanical response of outer cells could be influenced by the time constant of the cell, mainly because transmembrane AC receptor potentials will be greatly attenuated at high frequencies: this effect could theoretically limit the motor response, if this is only driven by receptor potential. Nonetheless, some mechanisms let the inner ear overcome the limiting effects of the membrane filter encountered for acoustic stimulation at high frequency: in fact, a role of a mechanically activated flux of chloride through the lateral plasma membrane is evident in the function of prestin *in vivo* (Rybalchenko et al, 2003), which could underlie a voltage independence; moreover, active mechanical responses of the stereocilia bundle may be driven by calcium

influx through mechanically activated calcium-sensitive channels, not limited by the membrane filter. The motor properties make the outer hair cells act as a cochlear amplifier: acting as both receptors and effectors, they are able to sense and enhance movements of the basilar membrane; in fact, contraction of outer hair cells enhances upward movement, whereas hair cell *elongation* accentuates the *downward* movement of the basilar membrane. Therefore, outer hair cells electromotility is necessary for sensitive hearing and sharp frequency discrimination. Hearing sensitivity and frequency selectivity are impaired by mutation of the gene for prestin or if outer cells are damaged (e.g., by some antibiotics) or absent.

The mechanical events originated in outer hair cells boost basilar membrane movements and enhance stimulus to the inner hair cells. The amplified upward movement of the basilar membrane forces endolymph to flow out from beneath the tectorial membrane, toward its tip; this flow causes the hair bundles of the inner hair cells to bend toward longer stereovilli, consequently opening transduction channels and depolarizing the cell. This depolarization opens voltage-gated Ca^{2+} channels, and the consequent rise of $[\text{Ca}^{2+}]_i$ induces synaptic vesicles fusion and glutamate release, depolarizing afferent neurons.

When the stapes moves inward, all described processes reverse as well: the basilar membrane bows downward, transduction channels close in the outer hair cells, which undergo *hyperpolarization* and cell elongation, accentuating downward movement of the basilar membrane which recalls endolymph back under the tectorial membrane; in this manner transduction channels close in inner hair cells, causing cell hyperpolarization and reduced neurotransmitter release.

3. ROLE OF NERVOUS SYSTEM

3.1. Auditory Nerve

The cochlea receives innervation from the auditory (or cochlear) nerve, a branch of cranial nerve VIII (Ruggero, 1982). Sensory cells somata (about 30,000) are found in the spiral ganglion and their dendrites contact nearby hair cells: 95% of neurons, termed type I cells, contact inner hair cells; the remainder afferent neurons, named type II, innervate the outer hair cells, which represent over three-quarters of the receptor cell population. The axons of afferent neurons project to the brainstem cochlear nucleus. A type I neuron generally contacts a single hair cell through a myelinated large and fast conducting fiber, thus their information reaches the brain within a few tenths of a millisecond; type II neurons, instead, sends processes to contact 5 to 100 outer hair cell by thin, unmyelinated and slow conducting fibers. Both afferent fiber types project centrally into the cochlear nucleus in the brain stem: inner hair cells and type I neurons are the main channel for sound-evoked information to reach the hierarchically upper structures in the brainstem, whereas outer hair cells contribute very little direct information about sound.

The stimulation with a continuous pure tone originates a wave which, travelling along the basilar membrane, has different amplitudes at different points along the base-apex axis. Hair cells are tuned to a certain frequency: their frequency sensitivity (or characteristic frequency) depends on their position along the basilar membrane of the cochlea, due either to the above-

described features of the basilar membrane, or to position-related structural differences between inner hair cells, enhancing the tuning. In fact, the ones near the base have shorter, stiffer stereovilli, which let them resonate to higher frequencies; on the contrary, the cells near the apex display longer and floppier stereovilli which make them resonate to lower frequencies; this position-based frequency selectivity of inner cells clearly describe a place coding of frequency. Aside, increases in sound *amplitude* cause an increase in the *rate* of action potentials in auditory nerve axons: then, sound intensity undergoes a rate coding at neuronal level, cooperation between neurons being required in order to code the full SPL range (0 to 120 dB SPL). The characteristic frequency of an acoustic nerve fiber is the frequency that evokes a response at the lowest sound pressure level, as low as 0 dB in the most sensitive range of hearing. The tuning curve, plotting the response area for a nerve fiber a graph of threshold sound pressure level vs. frequency, is extremely narrow at low sound levels, since the fiber responds only to a narrow band of frequencies near characteristic frequency, property likely linked to the active motility of the outer hair cells. The tuning curve is wider at high sound levels, in particular for frequencies below the characteristic frequency, likely reflecting most the passive mechanical characteristics of basilar membrane motion than outer hair cells electromotility. Fibers with the lowest characteristic frequencies innervate hair cells positioned at the cochlear apex, whereas fibers with higher characteristic frequencies contact hair cells located in progressively more basal regions, paralleling the pattern of basilar membrane vibration. This tonotopic mapping is preserved in the cochlear nucleus and along the central auditory pathway. Therefore, type I fibers respond to sound generating action potentials, often locked to particular phases within the cycle of the sound waveform following the phasic release of neurotransmitter depending by the AC receptor potential; both phase locking and AC receptor potential decrease for frequencies above 1 kHz.

Action potentials are then conducted toward the brain via discrete pathways which form a percept of the stimulus by extracting information about which nerve fibers are responding (place code, about frequency of sound, whereby neurons at different places code for different frequencies) and the rate and time pattern of the spikes in each fiber (information about sound intensity). Auditory nerve fibers with the same characteristic frequency show different sensitivity to sound intensity, and the difference between lower and higher thresholds can be as large as 70 dB. The sensitivity of response (SR) is correlated with the spontaneous firing rate of neurons, varying from one fiber to another over the range of 0 to 100 spikes/s. Three main groups of fibers have been classified on the basis of spontaneous firing: low SR (0.5 spikes/s), medium SR (0.5 to 17.5 spikes/s), high SR (17.5 spikes/s), the latter exhibiting higher sensitivities than the others. Low SR fibers play important roles in detecting changes in sounds at high intensities, because of both their low sensitivity, which causes them to respond mostly at high sound levels, and their lesser tendency to saturate. Information carried by the different SR groups may be kept somewhat separate in the brain stem: for example, low and medium SR fibers represent the largest afferents to the cochlear nucleus, preferentially innervating certain regions.

The response of a single auditory nerve fiber increases with sound level until it is saturated, that is to say the fiber no longer increases its firing rate. This mostly occurs within a dynamic range generally between 20 and 30 dB, sometimes greater. Such a narrow individual dynamic range does not match the large range in level of audible sound, from 0 to 100 dB. The auditory nerve can accurately signal within this large intensity range because fibers with the same characteristic frequency but lower sensitivity are recruited at higher

sound levels, when fibers tuned to other characteristic frequencies also begin to respond, since tuning curves become broader.

3.2. Descending Control on Inner Ear

The superior olivary complex of the brainstem projects fibers to the inner ear; in particular, lateral olivo-cochlear neurons, the function of which is not well known, contact dendrites of type I auditory nerve fibers through small diameter axons, whereas medial olivo-cochlear neurons project to outer hair cells through cholinergic fibers (Guinan, 1996; Warr, 1992).

Acetylcholine activates a nicotinic receptor on the membrane of the outer hair cell, allowing Ca^{2+} influx and K^{+} efflux through Ca^{2+} -activated K^{+} channels: in this manner the membrane results hyperpolarized, reducing the electromotility of the outer hair cell and the motion of basilar membrane; the responsiveness of inner hair cells and auditory nerve fibers is reduced and results shifted to higher sound levels. Consequently, this mechanism may control the gain of the cochlear amplifier to prevent saturation of responses, inducing suppression of responsiveness to unwanted sounds, protecting hair cells in the cochlea from damage due to intense sounds, and letting the fiber signal changes in sound intensity even at higher sound levels, being also able to underlie auditory focus in noisy environments.

3.3. Central Auditory Pathways

Starting from the cochlear nucleus, the auditory information travels toward the cerebral cortex via the thalamus, relaying in several brainstem nuclei with relevant functions (Rhode and Greenberg 1992). The cochlear nucleus is the best understood among auditory centers, being the region where parallel pathways in the auditory system begin. Cochlear nucleus neurons, excited by auditory nerve inputs, are classified following both morphological and functional criteria (tone burst-evoked firing pattern, map of response, laterality of response). On the basis of the *cellular firing patterns* in response to sound stimulation, cellular units in the cochlear nucleus are classified as “pauser” (pyramidal cells), “onset” (“octopus” cells), “primary-like with notch” (globular bushy cells), “chopper” (multipolar cells) and “primary-like” (spherical bushy cells). Like tuning curves, *response maps* plotted on graphs of sound level versus frequency show areas of excitation; however, they can also show areas of inhibition in the dorsal subdivision of the cochlear nucleus, the inferior colliculus, and at higher stages of the auditory system, since at these levels inhibitory influences are present, shaping responses. Five response types have been defined (types I-V) on this basis: type I responses have no inhibitory areas, the other types have progressively larger inhibitory areas. Type IV neurons correspond to pyramidal cells, the main projection neurons of the dorsal cochlear neuron. *Laterality of response* is defined as whether the neuron responds to the contralateral or ipsilateral ear and whether the response is excitatory or inhibitory. Many neurons in central auditory nuclei above the cochlear nucleus are binaural and can be influenced by sound presented to either ear. A predominant pattern, however, is for the neuron to be excited by sound in the contralateral ear, resulting from the fact that many

central auditory pathways cross to the opposite side of the brain. The influence of the ipsilateral ear can be excitatory, inhibitory, or mixed. There are also uncrossed pathways; these pathways generate the response to the ipsilateral ear. Despite an influence of the ipsilateral ear, lesion studies indicate the functional importance of excitation from the contralateral ear. For instance, damage to the inferior colliculus or auditory cortex on one side decreases the ability to localize sounds on the opposite side. Thus, as in other sensory and in motor systems, one side of the brain is concerned primarily with function on the opposite side of the body. An important characteristic of most central auditory nuclei is tonotopic organization, the mapping of neural characteristic frequencies onto position. This feature is determined by basilar membrane features and is relayed into the central nervous system by CN VIII, resulting in regions in which neurons share the same characteristic frequency, called isofrequency laminae.

The cochlear nucleus projects in turn to the other auditory nuclei of the brain stem: superior olivary complex, nuclei of the lateral lemniscus, and inferior colliculus, important for determination of the location of a sound source. In fact, whereas sound frequency is mapped along the cochlea, in contrast to other sensory systems the external location of a sound source is not directly represented in the auditory receptor organ. In the auditory system, directional information is centrally determined, mainly in the brain, by comparing interaural differences in responses.

The location of azimuthal position of sound sources in space is predominantly determined by the auditory system at the brain stem level, by using two main binaural cues, respectively interaural time differences and interaural level differences, differently useful depending on the frequency of the sound (Brand et al, 2002; Wightman and Kistler 1993; Yin and Chan 1990). Regarding the former, sound reaches the ear nearest to the source earlier than the farther one, markedly depending on the azimuth of the source: interaural time differences can be then translated into phase differences in the sound waveforms at the two ears, particularly useful at low frequencies; however, they become less affordable for frequencies >1.5 kHz because the time interval needed for the sound to reach the farther ear could be sufficient for the waveform to repeat by a cycle or multiples. A second reason for differences are less important for localizing sounds at high frequencies is linked to the decline in phase locking for frequencies above 1 to 3 kHz.

Interaural level differences are dependent on the *sound shadow* action exerted by the head, which reduces the level of sound at the ear away from the source. These differences are significantly large only at high frequencies, being much smaller at low frequencies. Thus, interaural time differences are the major cues for sound localization at low frequencies (1 kHz), whereas interaural level differences for localization at high frequencies (3 kHz). The accuracy of azimuthal localization is good at both low and high frequencies, being less accurate at middle frequencies because the cues are more ambiguous in this range. The minimum discriminable angle for localization of a sound source approaches one degree of azimuth, corresponding to about 10 ms in interaural time and 1 dB interaural level differences.

Two neural circuits that provide sensitivity to interaural time or level differences are within the superior olivary complex, respectively found in the medial (MSO) and in lateral superior olive (LSO), and their inputs.

Originated from both left and right cochlear nuclei, the afferents for the MSO of each side are from primary-like units (spherical bushy cells), the activity of which preserves the timing and phase-locking features of the auditory nerve fibers. For low frequency sounds joining from a lateral source, a time difference will exist between phase-locked spikes from one side relative to the ones of the other side. During a continuous sound, this time difference between phase-locked spikes will repeat for each of the many waveforms.

An impulse takes time to travel along a fiber, that is way an axon can be considered a *delay line*. In the model proposed by Jeffress, within the MSO neurons respond best when they receive coincident input from the two sides, if the delays were about equal. If we consider a series of neurons in the MSO, each receiving converging inputs from both cochlear nuclei in such a way that the afferents from each cochlear nucleus enter the series from opposite sides, we observe that, because of the same conduction speed in afferent fibers, neurons in the middle of the series can receive temporally coincident activation only when both cochlear nuclei are activated simultaneously, that is to say when sound simultaneously reach both ears because its source is located along the midline, equidistant from each ear. For sound sources located laterally to the midline, coincident activation will be received by neurons more laterally placed in the series: the topography of neurons receiving coincident activation is hypothesized to be the key mechanism allowing to exactly perceive the source location of a sound.

Neurons and circuits in the lateral superior olive (LSO) are sensitive to interaural level differences. LSO also receive bilateral inputs, excitatory from the ipsilateral side (joining from spherical bushy cells of the cochlear nucleus), whereas inhibitory from the contralateral side, in particular from globular bushy cells of the cochlear nucleus, and synapses on inhibitory neurons in the medial nucleus of the trapezoid body, which use the neurotransmitter glycine. LSO neurons compare the difference between sound levels at the two ears, being then excited when sound in the ipsilateral ear is of higher level, whereas inhibited when sound is of higher level in the contralateral ear. If sound is of equal level in the two ears, little neuronal response is observed because of a prevalent contralateral inhibition. These neurons are thus excited by sound sources located on the ipsilateral side of the head. The lateral superior olive projects centrally either excitatory fibers to the inferior colliculus on the opposite side, transforming this ipsilateral response to a contralateral one, or inhibitory fibers to the inferior colliculus of the same side. LSO is predominantly composed of neurons with high characteristic frequencies and has a tonotopic organization.

Almost all ascending inputs from lower brain stem centers converges at the inferior colliculus, a structure displaying several subdivisions. The *central nucleus* is organized tonotopically and receives direct input from the cochlear nucleus and binaural input from the MSO and LSO: the dorsolateral part of the nucleus receives low characteristic frequency input, included the one from MSO, whereas the ventromedial part is targeted by LSO and generally by high characteristic frequency fibers. In the colliculus, terminals from the MSO and LSO may have limited spatial overlap: due to the nature of the afferents, neurons in the dorsolateral part of the colliculus are mainly sensitive to interaural time differences, whereas cells in the ventromedial region of the nucleus are sensitive to interaural level differences. Since additional circuits for the generation of ITD sensitivity have not been identified, the colliculus appears to be sensitive to interaural time differences mainly by action of its inputs from the MSO. On the contrary, damaging the superior olivary complex does not abolish sensitivity to interaural level differences in the colliculus, which can be then created anew at

levels above the LSO, either by the dorsal nucleus of the lateral lemniscus, that sends a large inhibitory projection to the colliculus, or by inhibitory mechanisms within the colliculus. Differently from other specialized mammals, in the human auditory system there is no evidence of a mapping of sound source location to position within the inferior colliculus.

The inferior colliculus transmits auditory information to both the superior colliculus, where a spatial map of sound is found, and the auditory cerebral cortex: in particular, neurons of the inferior colliculus project to the medial geniculate body (de Ribaupierre, 1997), where principal cells in turn project to the auditory cortex. The pathways from the inferior colliculus include a lemniscal (*core*) pathway and extralemniscal (*belt*) pathways.

3.4. Auditory Cortex

The auditory cortex includes several areas of the dorsal temporal lobe (Clarey et al, 1992). The ventral region of the medial geniculate nucleus sends the main projection to the primary auditory cortex (A1, or Brodmann area 41), which in humans lies on Heschl's gyrus of the temporal lobe, medial to the sylvian fissure, and contains a tonotopic representation of characteristic frequencies, that is to say an organized map reflecting the pattern of peripheral sensors, based on the frequencies that best stimulate the neurons. In particular, neurons with low characteristic frequencies are located rostrally, whereas those tuned to high frequencies are found at the caudal end of A1. Then, a smooth frequency gradient is evident in one direction, whereas iso-frequency contours are observed along the orthogonal direction. Due to larger inputs, representations of relevant frequencies are wider in comparison with representations of other frequencies. Other characteristics of auditory stimuli are also represented in A1, with less clear mapping rules: for example, at right angles to the axis of tonotopic mapping, a map of binaural interactions is evident.

Like other cortical areas, the auditory cortex is organized in cortical columns running across all of the cortical layers and oriented normally to the cortical surface. All neurons within a column have similar response characteristics (e.g., similar characteristic frequencies and types of responses to binaural sounds): regarding the latter, generally a cortical neuron is excited by the main ear (most often the contralateral one), whereas the opposite ear can be excitatory (EE neurons) or inhibitory (EI neurons), respectively displaying a summation or a suppressive interaction; depending on sound level, some neurons can show both summation and suppression interactions. Summation columns alternate with suppression columns, mainly in the A1 high frequency region. Neurons within a summation column tend to have large projections to the opposite hemisphere, whereas fewer contralateral projections are generally sent by suppression columns, unless for columns with neurons inhibited by contralateral ear and excited by ipsilateral ear. Thus, the auditory cortex can be subdivided into cortical columns responsive to every audible frequency and each type of binaural interaction.

Others parameters mapped onto the surface of primary auditory cortex are bandwidth (responsiveness to a narrow or broad range of frequencies), neuronal response latency, loudness, etc. The intersection between different maps is not still understood. In every case, in A1 neurons and subregions many independent variables of sound are represented, which permit selective sound discrimination on the basis of several independent and/or combined analyses.

Multiple regions surround A1, many of which show a tonotopic representation. These areas receive direct input from the ventral division of the medial geniculate nucleus, primarily in cortical layers IIb and IV. Adjacent tonotopic fields have mirror-image tonotopy, since the direction of tonotopy reverses at the boundary between fields.

Actually, it is suggested by different Authors that primary or primary-like areas (*core*, 3 or 4 areas) are surrounded by 7 to 10 secondary areas (*belt*), the latter receiving input from the core areas of auditory cortex, as well as from thalamic nuclei, in some cases (Rauschecker et al, 1995). As revealed by recent functional MRI studies, in humans and monkeys core regions are primarily activated by pure tones, whereas complex sounds and narrow-band noise bursts activate the neurons of belt areas.

In the auditory cortex, many neurons with large receptive fields and broad tuning are sensitive to interaural time and level differences and therefore to spatial localization of sounds; however, no organized spatial map of sound is evident in any of the sound location sensitive cortical areas, differently from what observed in the midbrain (Buonomano and Merzenich, 1998; Cohen and Knudsen 1999). These cortical neurons sensitive to sound spatial location are found along a sound-localization pathway starting from the central nucleus of the inferior colliculus and reaching (through the auditory thalamus) the A1 area, cortical association areas and the frontal eye fields, involved in gaze control, which are directly connected to brain stem tegmentum premotor nuclei mediating gaze changes, as well as to the superior colliculus.

Cortical pathways are required for more complex sound-localization tasks (forming an image of the sound source, remembering it, moving toward it, etc.), being less active if the task is only to indicate the side of the sound source.

As for the output from the primary visual and somatosensory cortex, the circuits originating from the auditory cortex are segregated into separate processing streams. In fact, the more rostral and ventral areas connect primarily to the more rostral and ventral areas of the temporal lobe, generally implicated in nonspatial functions, whereas the more caudal area projects to the dorsal and caudal temporal lobe, implicated in spatial processing. In addition, these belt areas and their temporal lobe targets both project to largely different areas of the frontal lobes. Caudal and parietal areas are more active when a sound must be located or moves, and ventral areas are more active during identification of the same stimulus or analysis of its pitch. Therefore, an oversimplified schema suggests that identification of auditory objects could be made by anterior-ventral pathways by analyzing spectral and temporal characteristics of sounds, whereas dorsal-posterior pathways could analyze sound source location and detection of source motion.

As for both visual and somatosensory systems, the auditory cortex massively projects back to lower areas: the ratio between descending fibers entering the sensory thalamus and axons projecting from the thalamus to the cortex is almost 10:1. Fibers from the auditory cortex contact the inferior colliculus, olivo-cochlear neurons and the dorsal cochlear nucleus. Through these projections, the auditory cortex can actively increase and adjust the responses of neurons in subcortical structures, in this way modulating and sharpening signal processing. On the contrary, a decreased cortical activity reduces thalamic and collicular responses. Therefore, the cortex exercises a top-down control of perception.

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Chapter 54

GENETICS IN SENSORINEURAL HEARING LOSS

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ABSTRACT

In the field of genetics, this decade will be characterized by the widespread use of so-called next-generation sequencers, first described in 2003, based on the human genome project publication essentially conducted through Sanger sequencing using the first generation of DNA-sequencers. Actually, before long, there was a rapidly growing demand for a new system, thus a new generation of non-Sanger-based sequencing technologies have been developed to sequence DNA at an unprecedented speed, thereby enabling impressive scientific achievements and novel biological applications. The premises and promises of similar events open a window on a next generation diagnosis of hearing losses. However, this new technology has to overcome the inertia of a field that has previously relied on Sanger-sequencing for 30 years. These new methods of DNA analysis are promising and could considerably reduce the time and cost of sequencing studies, up to the famous spot “the genome for \$1,000”. However, the use of technology does not necessarily suggest an infallible diagnosis and optimal treatment. There is a need to “manage” a substantial amount of information (that at best will be different and complementary) to extrapolate meaningful or rather more valuable conclusions than previously obtained, as well as interpretations and the resolution of ethical and legal aspects paradoxically require increasing amounts of time and money to manage such situations. In addition, recent increasing scientific evidences are reevaluating the Lamarckian approach to hereditary conditions beside to the classical most famous Mendelian or Darwinian models. Even more surprising and is the advent of genetic therapy for an increasing number of diseases. In conclusion, all events seem to announce a revolutionary decade for future diagnosis and treatments of genetic hearing loss. In such exciting, but also complex, context, the clinical approach needs to focus on the best and simplest solution.

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In this chapter, a brief review and update about genetics of hearing loss will be reported in the light of those revolutionary events, in order to help and accompanied the reader in reflecting on the new role of clinician in a high rapidly changing context.

Keywords: genetics, hearing loss, syndromic hearing loss

INTRODUCTION

In the field of genetics, this decade will be characterized by the widespread use of so-called next-generation sequencers (Schuster 2008, Shaffer 2007), first described in 2003, based on the human genome project publication (2003) essentially conducted through Sanger sequencing using the first generation of DNA-sequencers. However, before long, there was a rapidly growing demand for a new system. Thus, a new generation of non-Sanger-based sequencing technologies have been developed to sequence DNA at an unprecedented speed, thereby enabling impressive scientific achievements and novel biological applications. However, this new technology has to overcome the inertia of a field that has previously relied on Sanger-sequencing for 30 years (Schuster 2008). To characterize the new “tools” available to geneticists, we should consider the following example: previously published literature has been passed from pen and inkwell to scanner and digital copier in less than ten years. With minor inconvenience, in the terms of the previous example, scanners were initially used to acquire only parts of a line at a time, and subsequently the need to recreate complete sentences, pages, chapters, books and libraries increased as a reference to allow this process. In addition, the “writers”, “readers”, “book-shops” and the original sources have not been completely adapted and remain based on older technology. However, these new methods of DNA analysis are promising and could considerably reduce the time and cost of sequencing studies, up to the famous spot sentence “the genome for \$1,000” (Dondorp and de Wert 2013). Unfortunately, possessing a fantastic scanner does equate with being an excellent photographer or writer, and similarly the use of technology do not necessarily suggest an infallible diagnosis and optimal treatment. Thus, there is a need to “manage” a substantial amount of information (that at best will be different and complementary) to extrapolate meaningful or rather more valuable conclusions than previously obtained, for example interpretations and the resolution of ethical and legal aspects paradoxically require increasing amounts of time and money. Ironically, bioinformatics replies to the “genome for \$1,000” spot with the “consequentially cost of \$1 million for data analysis” (Mardis 2010). How could this paradox be avoided? How does this paradox affect clinical practice in general or specific cases? Although the aim of this chapter is not to resolve controversial scientific (or philosophical) debates, it can be argued that physicians, patients and readers benefit from the knowledge that there are too many questions about privacy and too many doubts concerning the accuracy and in other words, the interpretation of this information.

Even when the clinical management and professionals involved are perfect, occasionally the genetics of hearing loss can generate confusion in patients, physicians and geneticists (also), likely reflecting the complexity and knowledge of the field (Salvago et al. 2014, De Stefano, Kulamarva, and Dispenza 2012). Indeed, a syndrome can be well known and well described (i.e., hearing loss, goiter, suggestive tonal and speech audiometries, CT/MRI scans with enlarged vestibular aqueducts and/or Mondini deformity, and positive perchlorate tests),

although it might be difficult to identify a mutation in the gene responsible for that condition (*SLC26A4*, and/or *FOXI1* and/or *KCNJ10*, etc.).

HEARING LOSS AND ITS GENETICS

Hearing impairment is one of the commonest clinical conditions, in particular at birth. It has been estimated that approximately 1-2 in 100 person has hearing concerns in the first decade of life (Martines et al. 2015, Dispenza, De Stefano, et al. 2013). The prevalence of childhood and adolescent hearing loss is around 3%. The causes of hearing loss differ and they can vary in severity and physiopathology: the etiology of hearing loss in children remains unknown in 30-40% of cases, non-genetic in 30-35%, genetic non-syndromic in 30%, and genetic syndromic in 3-5% (Bartolotta et al. 2014, Dispenza, Cappello, et al. 2013). Most of genetic conditions responsible for hearing loss appear in a non-syndromic form (60-75% of all genetic cases). The two most common genes involved in hearing loss are *GJB2* for the non-syndromic forms and *SLC26A4* the syndromic ones.

The main objective of correctly identifying a syndrome should only be the usefulness for the patients. If you have doubts or improper diagnostic instruments it would be more helpful to describe, more objectively as possible, all available clinical data. Giving a “name” should help patients in manage and communicate their conditions, promoting a multidisciplinary approach. It should be also remembered that there are not specialists or specialties that can singularly approach all syndromes, as well as there is no a syndrome that cannot keep advantage from all available specialties. Therefore, the main target should be investigating and exploring clinical and genetic conditions trying to bring benefits to whom that are suffering from. The correct diagnosis comes next.

Even if recent advances provide improvement in diagnosis, the most effective procedures to suspect a genetic cause of hearing loss still remains history and objective clinical examination essentially based on: 1) family history; 2) symmetry of clinical findings (bilateral hearing loss); 3) dysmorphic features 4) symptoms onset and/or progression.

Non-Syndromic Hearing Loss (Approximately 65% of All Genetic Causes of Hearing Loss): Audioprofiles of Dominant and Recessive Patterns

More than 60 genes have been so far associated with non-syndromic hearing loss. Mutations in the *GJB2* gene still remain the leading cause of non-syndromic sensorineural hearing loss on a genetic basis; however today the new NGS panels modify the number of mutations identified in a more varied and wide gene range, including *TMC1* and *TECTA* for example. A new useful approach especially for the non-geneticist specialist may be to consider audioprofiles in different transmission patterns: non-syndromic dominant (sexual or autosomal chromosomes), non-syndromic recessive (sexual or autosomal chromosomes) and mitochondrial. The definition of a specific audioprofile for genes and mutations provides a good genetic knowledge without neglecting the clinical contribution and consists practically in collecting clinical data (in essence they are condensed in the audiometric data being non-syndromic forms, or in any case of a single organ, ear in this case) of all patients with similar

mutations matched by age and when possible also by sex. Obviously for these case history is essential and collecting data revealed interesting considerations: in most cases non-syndromic with recessive patterns show worse entity of hearing loss without a slow progression, with early symptoms onset; in contrast dominant pattern has less severe loss of hearing, but high rate of progression with late onset. A deepening of these topics concerns the residual function of the proteins that has been widely found in the truncating and non-truncating forms of connexin 26 with important correlations and responses on the clinical clinic. However, as desirable, it would be quite challenging to evaluate and estimate the residual function of mutated proteins for each gene potentially involved in hearing loss, in addition to the difficulty in collecting an adequate number of identical mutations for each gene.

Syndromic Hearing Loss, without Congenital Craniofacial Findings and Recessive Inheritance Pattern

Even if initial screening examinations indicate normal hearing, the child remains at risk. During infancy and early childhood, parents should be aware of, and questioned about, the child's hearing and language milestones. Some syndromes, such as Pendred, Alport, Refsum, neurofibromatosis type II, Usher, and osteopetrosis, may place the patient at risk for progressive hearing loss.

Pendred Syndrome (Prevalence 7,5:100000, approximately 5% of Cases of Congenital Hearing Loss), otherwise the FOXI1-SLC26A4/ KCNJ10 Genetic Variants Responsible for Ions Disorders in the Inner Ear)

Two clinical pictures come from mutations in the *SLC26A4* gene: (1) the syndromic form, called Pendred Syndrome, characterized by hearing loss, goiter and eventually hypothyroidism, with/without EVA or other inner ear malformations as Mondini deformity; (2) the non-syndromic form, called DFNB4 or non-syndromic EVA (when EVA is present), characterized by hearing loss with/without EVA or other inner ear malformations. Mutations in the *FOXI1* (5q34) gene can be also responsible for these conditions. *FOXI1* encodes for a transcriptional activator that allow the transcription of *SLC26A4* and it is fundamental to develop normal sense of hearing and balance. Furthermore, mutations in the inwardly rectifying K (+) channel gene *KCNJ10* (1q23.2) can be also associated with hearing loss in carriers of *SLC26A4* mutations. The inner ear malformations, when present, are generally bilateral (even if unilateral involvement is not exceptional), and they not seem to affect the auditory rehabilitation through cochlear implantation (Benatti et al. 2013, Busi et al. 2012, Busi et al. 2015, Castiglione, Busi, and Martini 2013, Castiglione et al. 2014).

The type of hearing loss is mixed and variable from moderate to profound; the hearing impairment can be progressive and affected patients can benefit from binaural or bimodal auditory training with hearing aids or cochlear implantation. Considering the progression of the disease required a planning in prescribing auditory device that takes into account this concrete possibility. Even if a conductive component can be present, generally patients do not

take advantages from bone conduction devices (Benatti et al. 2013, Busi et al. 2012, Busi et al. 2015, Castiglione, Busi, and Martini 2013, Castiglione et al. 2014).

Usher Syndrome (Ciliopathies Reflecting the Potential Effects of Variations in the Genes Encoding Actin-Based Structures and Tip Links in Inner Ear Cells)

There are 3 types of Usher Syndrome and 10 subtypes, which altogether account for the diagnosis of 3.5 cases per 100,000 births. Thus, this syndrome is one of the most common illnesses after Pendred Syndrome, characterized by hearing loss without major dysmorphic aspects. The genetics of Usher Syndrome are complex, reflecting the high number of genes potentially involved in this condition: *MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *SANS*, *USH2A*, *VLGR1*, *WHRN*, *USH3A*, and *PDZD7* (Reiners et al. 2006). The majority of these genes are involved in the formation and constitution of specific structures (called tip-link) and actin filaments in inner ear cells. Notably, the cilia outside of the inner ear typically composed of tubulin (not actin); therefore, these structures are preserved in Usher Syndrome. However, syndromes that show similar aspects, such as Alström Syndrome, could result from mutations in genes encoding proteins and elements common to actin and tubulin, suggesting a wide clinical spectrum (and more severe) in Alström Syndrome. The retinal pigment epithelium contains both actin and tubulin filaments essential for melanosome activity. Retinitis pigmentosa in Usher and Alström Syndromes results from defects in actin and/or tubulin in the retinal pigment epithelium or photoreceptors.

Patients with Usher Syndrome develop hearing loss and vestibular and visual impairments. This disorder is inherited in an autosomal recessive pattern and characterized by progressive blindness resulting from retinitis pigmentosa, and moderate to severe sensorineural hearing loss. Usher syndrome has been classified into three types: Type I, characterized by severe to profound bilateral congenital hearing loss and poor or absent vestibular function with retinitis pigmentosa diagnosed by 10 years of age; Type II, characterized by mild to moderate hearing loss at birth and normal vestibular function with the onset of retinitis pigmentosa during late adolescence; Type III, characterized by progressive hearing loss and vestibular dysfunction with a variable degree of retinitis pigmentosa (Castiglione, Busi, and Martini 2013). Due to the lacking of visual reinforcement in spatial orientation, these patients can benefit from mandatory binaural auditory rehabilitation, when not contraindicated, with hearing aids or cochlear implants.

Jervell and Lange-Nielsen Syndrome (Prevalence 0.3: 100,000), or Genetic Variants of KCN1/KCNE1 Genes Responsible for Ions Disorders in the Inner Ear

Prolongation of the QT interval can come out from genetic defects in channel proteins, the same proteins that can be responsible for sensorineural hearing loss when expressed in the inner ear. These channels are critical in the function of the inner ear and heart muscle. The prolonged QT has the higher prevalence among this patients, and then is called Jervell and

Lange-Nielsen syndrome when (and only if) it is accompanied by hearing loss; thus, by definition, 100% of patients have hearing loss that tends to be severe to profound. Mutations in the *KCNQ1*, and less commonly, the *KCNE1* gene, coding proteins that form potassium transport channels, are considered responsible for the Jervell and Lange-Nielsen syndrome.

Syndromic Hearing Loss with Congenital Craniofacial Findings and Dominant Inheritance Pattern

Describing morphological and clinical aspects still remains the best clinical practice involving the precise, thorough and accurate collection of signs and symptoms, suggesting that the accurate diagnosis of a syndrome is not an intuitive reaction when examining a patient. Indeed, patients must be examined from different point of views: frontal, lateral and ventral. Examiners must not estimate abnormalities through sight, but rather anomalies should be measured using appropriate instruments. These analyses should proceed stepwise, combining until the obtained knowledge facilitates the consideration of clinical aspects other specialists have previously described or defined. Useless tests or exams and needless considerations of all available tests for patients should be avoided. Even when the diagnosis seems accurate, 2-3 alternative solutions should also be considered to avoid misdiagnosis. Notably, having a mutation does not prevent the occurrence of other diseases, conditions or genetic disorders. In most cases, it is possible to hypothesize fragility in DNA repair or function, even when difficult to prove, thus a collection of different mutations could affect the phenotype.

BOR Syndrome and EYA1 Related Disorders (or Branchial Defects Potentially Resulting from Genetic Variants in EYA1, SIX5, and SIX3, Genes on the Axis of the Tbx1-Six1/Eya1-Fgf8 Genetic Pathway)

Branchio-oto-renal (BOR) syndrome is an autosomal dominant disorder comprising external, middle and inner ear malformations, branchial cleft sinuses, cervical fistulae, mixed or conductive hearing loss and renal anomalies with an estimate prevalence of 2-3:100000 newborns, responsible for approximately 2% of deaf children. BOR syndrome is perhaps one of the most frequent syndromes responsible for hearing loss, with most difficulties in defining and performing auditory rehabilitation. With respect to syndromes in otolaryngology, the BOR disorder represents the first ones among congenital malformations (together with the Treacher Collins syndrome). Furthermore, BOR syndrome is perhaps one with the widest clinically variable diseases with uncertain auditory assessment and rehabilitation. The best advice in these cases is to exclusively to rely on audiometric profiling and patient impressions, as there is no clear correlation between the observed malformations and the severity of hearing loss. Notably, all associated congenital conditions, mild or moderate, represent the natural hearing for these patients. Therefore, external interventions (surgery or hearing aids) might be considered “artificial” and “unacceptable”. Indeed, experts must perform reconstructive surgery on the middle and external ears, and the results in terms of auditory function can be extremely disappointing, if not pejorative.

BOR syndrome primarily reflects mutations in *EYA1* (on chromosome 8, BOR type 1) *SIX5* (on chromosome 19, BOR type 2) and *SIX1* (on chromosome 14, BOR type 3) genes, although we cannot exclude the involvement of other genes that play a role in the *Tbx1-Six1/Eya1-Fgf8* genetic pathway, which controls mammalian cardiovascular and craniofacial morphogenesis, as demonstrated for other branchial defects, such as Di George syndrome (Guo et al. 2011).

CHARGE Association (or Overlapping Features with DiGeorge Syndrome and Other Branchial Defects Resulting from Genetic Variations in the SMAD1/CHD7-FGF8/BMP Family/WNT1-OTX2-FOXA2-TBX1 Genetic Pathways)

When considering genetic hearing loss, the possibility of sharing new pathways with other syndromes should be considered, suggesting that these defects can be surprisingly similar (or different) (Corsten-Janssen et al. 2013, Guo et al. 2011, Liu et al. 2014, Payne et al. 2015, Schulz et al. 2014).

CHARGE association or syndrome has a birth prevalence of approximately 0.14 per 100,000 newborns. The acronym recalls the primary clinical manifestations of this syndrome, although the corollary of signs and symptoms are much more vast and complex, including iris or retinal colobomas, heart disease, choanal atresia, growth defects and developmental delays, genitourinary hypoplasia, external ear abnormalities, brain abnormalities, sensorineural hearing loss (up to 90% of cases), respiratory problems and cranial nerve hypoplasia (including the seventh and the eighth ones) with important functional deficits. This association reflects mutations in the *CHD7* gene in approximately two thirds of cases. The CHARGE association alone it is not an absolute limit to the rehabilitation program; indeed, expectations must be consistent with the clinical conditions, and in cases of cochlear implant, the expert medical team will generate nerve stimulation, and carefully evaluate hypoplasia and malformations. Bilateral or binaural rehabilitation is desirable.

Mutations in the MITF Pathway (Responsible for Waardenburg Syndrome)

The *MITF* promoter is partially regulated through the transcription factors *PAX3*, *SOX10*, *LEF1/TCF* and *CREB* during melanocyte development. In humans, mutations affecting the *MITF* pathway lead to pigmentary and auditory defects, collectively known as Waardenburg Syndrome (WS) (Lin and Fisher 2007). The *MITF* gene encodes a transcription factor that regulates the differentiation and development of melanocytes and the retinal pigment epithelium and is also responsible for the pigment cell-specific transcription of melanogenesis genes. Hearing deficiency stems from a requirement for melanocytes within the stria vascularis of the cochlea (inner ear), a requirement involving the maintenance of endolymphatic potassium for auditory nerve action potential. Waardenburg-associated mutations represent a striking epistatic series in which essentially every culprit gene is mechanistically associated with the regulation of *MITF* expression or activity. These genes, including *Pax3*, *Slug*, *Sox10*, endothelin 1, and endothelin receptor B, are transcriptional

regulators of *MITF* expression (Pax3 and Sox10), transcriptional targets of *MITF* (Slug), or *MAPK* activators that directly phosphorylate *MITF* (ET1 and EdnrB) (Steel 1995, Chin, Garraway, and Fisher 2006). Mutations in *MITF* gene are also responsible for melanomas, but these mutations typically differ in type and effect from those causing pigmentary defects and deafness, thus leading to different phenotypes (Grill et al. 2013).

CONCLUSION: PERFORM SIMPLE TASKS WITH THE HIGHEST ATTENTION

In 2013, Stamatiou GA and Stankovic KM (Stamatiou and Stankovic 2013) published a fine analysis on a new point of view during the present new era of NGS to identify “genetic nodes” of several genes. The genes associated with hearing loss and deafness were identified through PubMed literature searches and the Hereditary Hearing Loss Homepage. These genes were assembled into 3 groups: 63 genes associated with nonsyndromic deafness, 107 genes associated with nonsyndromic or syndromic sensorineural deafness, and 112 genes associated with otic capsule development and malformations. Each group of genes was analyzed to identify the most interconnected nodal molecules. The nodal molecules of these networks included transforming growth factor beta1 (*TGFB1*) for Group 1, *MAPK3/MAPK1* MAP kinase (*ERK 1/2*) and the G protein coupled receptors (*GPCR*) for Group 2, and *TGFB1* and hepatocyte nuclear factor 4 alpha (*HNF4A*) for Group 3. These results were confirmed in different analyses, suggesting new investigations and treatments involving glutathione, protein kinase B (Akt) and nuclear factor kappa B (NFkB) (Muller and Barr-Gillespie 2015).

A potential solution for more demanding genetic analyses could involve separating the multitude of genes in variously articulated pathways of different lengths, assigning priority when possible, and subsequently analyzing these pathways, moving on to the next series when a non-conclusive mutation is identified; these analyses must continue until the changes that greatly impact pathological pathways are identified.

Not only wide analyses but also targeted analyses should be performed, and impacted pathways should be developed and designed, considering the clinical and diagnostic possibilities. At this point the quality of a pathway is fundamental and should be well known and defined as the metabolic pathway. Obviously, a long period of study and analysis to identify genetic variations (pathological conditions) is needed, as the cause-effect relationship does not always exhibit a desirable time of onset, and frequently, only the initial effects associated with disease causes are observed.

However, a genetic pathway is not always as linear as a classical metabolic pathway, rather metabolic pathways can be “modified” in different ways, whereas a genetic pathway can be “far” from linear, with sequential events, also influenced through time and the environment. Thus, the clinical phenotype is markedly helpful in defining the depth of the associated analysis.

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Chapter 55

CONGENITAL SENSORINEURAL HEARING LOSS

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ABSTRACT

Congenital hearing loss (CHL) is defined as the hearing loss present at birth and, consequently, before speech development. It is one of the prevalent chronic conditions in children and the main sensor neural disorder in developed countries. The estimated prevalence of permanent bilateral CHL is 1-3 per 1000 live births in developed countries.

CHL is caused by genetic factors in more than 50% of the cases. Genetic hearing loss may be the only clinical feature (non-syndromic or isolated forms) or may be associated with other symptoms (syndromic forms).

Non-syndromic hearing loss is extremely heterogeneous. About 80% of the cases are autosomal recessive, 15-24% are autosomal dominant and 1-2% are X-linked. Furthermore, less than 1% of CHL resulting from mitochondrial mutations and it presents with a characteristic matrilineal pattern of transmission. Typically, autosomal recessive hearing loss is congenital whereas autosomal dominant is often progressive. The most frequent isolated form of genetic hearing loss in white population of Europe and United States is the gap junction protein beta 2 gene (GJB2) mutation that is the gene encoding connexin-26.

Syndromic form represents about the 30% of the cases of CHL and literature reports more than 400 syndromes where hearing loss is accompanied with physical or laboratory findings. Responsible genes are known for many of these scenarios.

A genetic diagnosis is required for different reasons, in particular for choosing appropriate therapeutic options, for treating associated medical problem (syndromic forms) and for predicting the progression of the degree. New treatments and screening strategies are available for identifying the responsive gene, e.g., Next Generation DNA sequencing that allows the simultaneous analysis of a large number of genes causing CHL with a higher probability of gene identification.

This paragraph will describe the different genes and clinical features involved in CHL both in isolated and in syndromic form.

Keywords: congenital hearing loss, genetic hearing loss, deafness

INTRODUCTION

Congenital hearing loss (CHL) is defined as the hearing loss present at birth and, consequently, before speech development.

It is one of the prevalent chronic conditions in children and the main sensor neural disorder in developed countries.

The estimated prevalence of permanent bilateral CHL is 1-3 per 1000 live births in developed countries and it varies between 19-24 newborns in sub-Saharan Africa and South Asia respectively.

The prevalence of the hearing loss increase until 3-4 per live birth [1] during the first 5 years of life when considering the progressive hearing loss genetically programmed.

Late diagnosis or treatment has consequences on different child developmental area. CHL affect speech development, language acquisition and it has an impact in brain plasticity and cognitive development. The hearing impairment, if it is not properly treated, move to isolating themselves to society and may decrease work opportunity in adult life.

For these reasons, it is very important an early diagnosis and an early right treatment of the CHL. Universal newborn hearing screening program has allowed a reduction of the time of reimbursement of the child with different type and degree of deafness and a consequent reduction of the associated disabilities.

Moreover, different economic studies underline that untreated hearing loss has a high social cost during the life (e.g., in the USA amount to \$1.1 million for person) and this cost decrease by 75% in case of early intervention and treatment [2]. Schulze-Gattermann showed that pediatric cochlear implantation provides positive cost-benefit ratios compared with hearing aid users especially if the child is implanted before the age of 2 years [3].

The benefits are not only economic but also in quality of life and school cost (moreover in country where there are special school for deaf people) [4].

Psychological reaction to a cochlear implant (CI) may be influenced by the temperament of the implanted subject [5].

More than 50% of the CHL is caused by genetic factors but it is difficult found the specific etiologic diagnosis. In fact, may be only one mutation in a specific gene or different mutations in different genes. Moreover may be an association with environmental prenatal factors (e.g., infections, prematurity, neonatal intensive care unit recovery).

Genetic hearing loss may be the only clinical feature (non-syndromic or isolated forms) or may be associated with other symptoms (syndromic forms).

Approximately 30% of the CHL considered syndromic and the remaining 70% being non-syndromic.

Non-syndromic hearing loss is extremely heterogeneous. About 80% of the cases are autosomal recessive, 15-24% are autosomal dominant and 1-2% are X-linked.

Typically, autosomal recessive hearing loss is congenital whereas autosomal dominant is often progressive.

The loci linked to non-syndromic CHL are conventionally named using a prefix followed by a suffix integer: DNFA for autosomal dominant loci, DFNB for autosomal recessive loci and DFN for X-linked loci.

The syndromic form can be differentiated from nonsyndromic hearing loss by the presence of associated symptoms in other organ systems. Syndrome that involve hearing loss are currently more than 400 and in some cases deafness is not present at birth but it appears later.

Know the different gene implicated in hearing loss is very important because it allows to give information, at the proband and his family, with specific genetic counselling about prognosis and recurrence. A genetic diagnosis is required also for choosing appropriate therapeutic options, for treating associated medical problem (in syndromic forms) and for predicting the progression of the degree.

Researcher and clinicians can always be informed about gene implicate in CHL (number, mutation and loci) consulting the Hereditary Hearing loss Homepage (<http://hereditaryhearingloss.org>) or <http://ghr.nlm.nih.gov>.

New treatments and screening strategies are available for identifying the responsive gene, e.g., Next Generation DNA sequencing and genetic panels that allow the simultaneous analysis of a large number of genes causing CHL with a higher probability of gene identification.

This paragraph will describe the different genes and clinical features involved in CHL both in isolated and in syndromic form.

NON SYNDROMIC CHL

Non Syndromic CHL_Autosomal Recessive Hearing Loss

The loci and genes for non-syndromic, autosomal-recessive deafness are presented in Table 1.

Table 1. Genes related with autosomal recessive non-syndromic congenital hearing loss

Locus	Gene	Chromosomal Location	Protein	Function
DFNB1	GJB2 GJB6	13q11–q12	Connexin 26 Connexin 30	Gap junction (ion haemostasis)
DFNB2	MYO7A	11q13.5	Myosin VIIa	Transport
DFNB3	MYO15	17p11.2	Myosin Xva	Transport
DFNB4	SLC26A4	7q31	Pendrin	Acid-base balance of endolymph (ion haemostasis)
DFNB5		14q12		
DFNB6	TMIE	3p21		
DFNB7	TMC1	9q13–q21		
DFNB8	TMPRSS3	21q22.3		
DFNB9	OTOF	2p23.1	Otoferlin	Fusion of synaptic vescicle with Ca^{+2}
DFNB10	TMPRSS3	21q22.3		
DFNB11		9q13–q21		

Table 1. (Continued)

Locus	Gene	Chromosomal Location	Protein	Function
DFNB12	CDH23	10q21–q22	Cadherin 23	Lateran and tip links (adhesion)
DFNB13		7q34–q36		
DFNB14		7q31		
DFNB15		3q21.3–q25.2/19p13.3–p13.1		
DFNB16	STRC	15q15	Stereocilin	TM attachment links (adhesion)
DFNB17		7q31		
DFNB18	USH1C	11p15.1	Harmonin	Scaffolding protein (adhesion)
DFNB20		11q25–qter		
DFNB21	TECTA	11q23–q25	α -tectorin	Stability and structure of TM
DFNB22	OTOA	16p12.2	Otoancorin	TM attachment to nonsensory cell (adhesion)
DFNB23	PCDH15	10q21.1	Protocadherin 15	Lateran and tip links (adhesion)
DFNB27		2q23–q31		
DFNB29	CLDN14	21q22.1	Claudin 14	Tight junction
DFNB30	MYO3A	10p11.1	Myosin IIIA	Transport
DFNB31	WHRN	9q32–q34	Whirlin	Scaffolding protein (adhesion)
DFNB32		1p22.1–p13.3		
DFNB33		9q34.3		
DFNB35		14q24.1–q24.3		
DFNB36	ESPN	1p36.3	Espin	Actin crosslinking and bundling
DFNB37	MYO6	6q13	Myosin VI	Regulation of exocytosis, stereocilia anchoring
DFNB38		6q26–q27		
DFNB39		7q11.22–q21.12		
DFNB40		22q11.21–q12.1		
DFNB42		3q13.31–q22.3		
DFNB44		7p14.1–q11.22		
DFNB46		18p11.32–p11.31		
DFNB48		15q23–q25.1		
DFNB49	TRIC	5q12.3–q14.1	Tricellulin	Tight junction
DFNB53	COL11A2	6p21.3	Type XI collagen $\alpha 2$	Stability and structure of TM
DFNB55		4q12–q13.2		
DFNB91	GJB3	1p35–p33	Connexin 31	Gap Junction (ion haemostasis)

GJB2 (Connexin 26) – DFNB1A

The most frequent isolated form of genetic hearing loss in white population of Europe and United States is the gap junction protein beta 2 gene (GJB2) mutation that is the gene encoding connexin 26. Mutations in the GJB2 gene are responsible for as much as 50% of pre-lingual, recessive deafness.

GJB2 gene is located on chromosome 13q11 (DFNB1) and it was described for the first time in 1994 but the first mutation in the locus were observed in 1997 [6].

Connexins are a large family of protein with four transmembrane domains, which have been implicated in gap-junctional intercellular communication. Connexins are membrane proteins and core components of gap junctions (GJs), which are intercellular communication channels that are important for recycling potassium ions from the hair cells to the endolymph during auditory transduction.

These proteins are present in the cell membranes of the epithelial cells and connective tissue of the cochlea and are responsible for maintaining an electrical potential in the cochlea thanks to an exchange of neurotransmitters, metabolites and potassium ions [7].

Gene inheritance are autosomal recessive in most cases; however, there are been reported forms with a autosomal dominance pattern of inheritance [8].

More than 300 mutations in the GJB2 gene are reported in the literatures and some of these are observed in various population: 35delG mutation in the Caucasian population, 235delC in the Asian population, 167delT in the Jewish population and p.Trp24 in population of India, Bangladesh, Slovenia and Romania.

Incidence varies in the different European country: it is highest in the Mediterranean country and lowest in the north. In fact, c.35delG allele accounted for 65.5% of mutated chromosomes in the south of Italy [9-11].

The 35delG mutation consists of a deletion of a guanine (G) in a sequence of six Gs extending from position 30–35 leading to a frameshift and premature stop codon at nucleotide 38 [12, 13].

GJB2 mutations are correlated to a neurosensorineural hearing loss of different degree dependent on genotype. It has been show that patients with two truncating mutations have significantly more severe hearing impairment than truncating/missense compound heterozygotes and that patients with two missense mutations have even less hearing impairment [14, 15].

GJB6 (Connexin 30) – DFNB1B

In the same locus of the GJB2 mutation (DFNB1), another gene, related to congenital hearing loss, has been found: GJB6.

Also this gene encoding for a gap-junction protein, connexin 30 (Cx30), that is expressed in the same inner-ear structures as connexin 26. In fact, both connexins are functionally related and Cx30 is co-expressed with Cx26 in the fibrocytes of the spiral ligament, basal cells of stria vascularis, spiral limbus, and supporting cells in the organ of Corti [16-18].

Genetic transmission is autosomal recessive and can be connected to either two GJB6 deletions (rare) or one GJB6 deletion and one GJB2 variant on opposite chromosome [19].

Mutation in Connexin 30 is characterized by bilateral and stable prelingual, mild-to-profound sensorineural hearing impairment and affected individuals have no other associated medical findings.

MYO7A (Myosin VIIA) – DFNB2

Myosins are a family of actin-based molecular motors that use energy from hydrolysis of ATP to generate mechanical force.

The function of the unconventional myosins is to regulate intracellular membrane traffic.

The MYO7A gene is a typical unconventional myosin consisting of 48 coding exons that is express in cochlea and in the retina of the mammalian.

Phenotype presentation is characterized by both vestibular dysfunction and hearing loss because in the inner ear, only the cochlear and vestibular sensory hair cells expressed the myosin VIIA gene.

Deafness is non-syndromic, congenital, profound and it is transmitted in autosomal-recessive manner [20].

MYO15A (Myosin XV) – DFNB3

MYO15A is a part of myosin family. In the inner ear, it has the function of the transportation of different proteins.

Mutation in this gene leads to a profound congenital hearing loss [21].

SLC26A4 (Pendrin) – DFNB4

Mutations in the *SLC26A4* gene are reported to be the most frequent cause of hereditary hearing loss in East Asia, and the second most common cause worldwide, after Connexin 26 (*GJB2*) gene mutations.

Mutations in the *SLC26A4* gene are associated with two clinical pathway: Pendred syndrome or autosomal recessive non-syndromic deafness (DFNB4). Because of the variable expressivity and overlap of the clinical features, the two conditions may be considered as subsets of the spectrum of clinical manifestations of one single genetic entity.

Both disorders have similar audiologic characteristics which may be associated with abnormalities of the inner ear. In Pendred syndrome besides congenital sensorineural deafness, goiter or thyroid dysfunctions are frequently present.

The temporal bone abnormalities ranging from enlarged vestibular aqueduct (EVA) to Mondini dysplasia. To explain these abnormalities, it has been hypothesized that *SLC26A4* controls fluid homeostasis in the membranous labyrinth, which in turn affects development of the bony labyrinth.

Hearing loss is common bilateral, often severe to profound degree with prelingual onset but, in some case deafness can arise in late childhood to early adulthood.

SLC26A4 gene encodes a transmembrane protein, pendrin, which functions as a transporter of chloride and iodide.

The human pendrin is expressed in the inner ear, mainly in endolymphatic sac and hair cells, and in the follicular cells of the thyroid.

Impaired function of pendrin was associated with endolymph acidification, leading to auditory sensory transduction defects. It is believed that its function in normal inner ear is related to pH homeostasis whereas in the thyroid, have a function in electroneutral iodide/chloride exchanger [22, 23].

OTOF (Otoferlin) – DFNB9

Mutations in the *OTOF* gene cause two disorders: nonsyndromic prelingual deafness and less frequently, temperature-sensitive nonsyndromic auditory neuropathy/dys-synchrony.

In auditory neuropathy auditory brain stem responses (ABRs) are absent and otoacoustic emissions (OAEs) are present but, however, with time OAEs disappear.

Deafness is bilateral, prelingual onset and with severe to profound degree and without inner-ear anomalies.

Otoferlin gene encoding for a transmembrane domain at the C-terminus predicted to have a cytoplasmic location and three Ca²⁺-binding C2 domains. A function in Ca²⁺-triggered synaptic vesicle membrane fusion was hypothesized [24].

CDH23 (Otocadherin) – DFNB12

The CDH23 gene is a very large gene that encodes for an intercellular adhesion protein (Otocadherin).

The study of Astuto et al. has been show that the DFNB12 phenotype demonstrated a large intra- and interfamilial variation, with hearing loss ranging from moderate to profound deafness and age at diagnosis between 3 months and 6 years [25].

USH1C (Harmonin) – DFNB18

The USH1C gene encodes a PDZ domain-containing protein, harmonin detecting in the sensory areas of the inner ear, especially in the cytoplasm and stereocilia of hair cells.

Mutations in this gene were described to cause congenital profound, non-syndromic, sensorineural deafness and severe balance deficits.

Alteration in USH1C gene is related to Usher syndrome the most frequent cause of combined deaf-blindness in man [26].

TECTA (α -Tectorin) – DFNB21

TECTA encodes α -tectorin, one of the major non-collagenous extracellular matrix components of the tectorial membrane that bridges the stereocilia bundles of the sensory hair cells. For this reasons, mutations in this gene have a dominant-negative effect that disrupts the structure of the tectorial membrane.

Mutations in the TECTA gene have been shown to be responsible for both autosomal dominant nonsyndromic hearing impairment and autosomal recessive sensorineural prelingual non-syndromic deafness [27].

COL11A2 (Collagen 11 α 2) – DFNB53

COL11A2 protein encodes the collagen type XI alpha-2. Mutations in this gene cause a non syndromic profound hearing loss can it be non-syndromic autosomal-dominant or autosomal-recessive [28].

Non Syndromic CHL Autosomal Dominant Hearing Loss

On the contrary that the autosomal-recessive forms of deafness, autosomal-dominant forms are usually post-lingual and progressive [29].

The loci and genes for non-syndromic, autosomal-dominant deafness are presented in Table 2.

Table 2. Genes related with autosomal dominant non-syndromic congenital hearing loss

Locus	Gene	Chromosomal Location	Protein	Function
DFNA1	DIAPH1	5q31	Diaphanous 1	Actin polymerisation (cytoskeleton)
DFNA2	KCNQ4 GJB3	1p34	KCNQ4 Connexin 31	Voltage-gated K ⁺ channel Gap Junction (ion haemostasis)
DFNA3	GJB2 GJB6	13q12	Connexin 26 Connexin 30	Gap Junction (ion haemostasis)
DFNA4	MYH14	19q13	Nonmuscle myosin heavy chain XIV	Transport
DFNA5	DFNA5	7p15		
DFNA6	WFS1	4p16.3	wolframin	
DFNA7		1q21-q23		
DFNA8/12	TECTA	11q22-q24	A-tectorin	Stability and structure of TM
DFNA9	COCH	14q12-q13	Cochlin	Structures of the spiral limbus
DFNA10	EYA4	6q22-q23	Eyes absent 4	Regulation of transcription
DFNA11	MYO7A	11q12.3-q21	Myosin VIIa	Transport
DFNA13	COL11A2	6p21	Type XI collagen α 2	Stability and structures of TM
DFNA14	WFS1	4p16.3	wolframin	
DFNA15	POU4F3	5q31	Class 3 POU	Regulation of transcription
DFNA16		2q23-q24.3		
DFNA17	MYH9	22q12.2-q13.3	Non muscle myosin heavy chain IX	transport
DFNA18		3q22		
DFNA20/26	ACTG1	17q25	γ -actin	Building cytoskeleton
DFNA21		6p21-p22		
DFNA22	MYO6	6q13	Myosin VI	Regulation of exocytosis, anchoring stereocilia
DFNA23		14q21-q22		
DFNA24		4q35-qter		
DFNA25	SLC17A8	12q21-q24	VGLUT-3	Regulation of exocytosis and endocytosis of glutamate
DFNA28	TFCP2L3	8q22	Transcription factors CP2-like 3	Regulation of transcription
DFNA30		15q25-q26		
DFNA36	TMC1	9q13-q21		
DFNA38	WFS1	4p16	wolframin	

DIAPH1 (Diaphanous) – DFNA1

Expression of DIAPH1 gene was demonstrated in many tissues including cochlea and skeletal muscle.

The gene *DIAPH1* is involved in cytokinesis and establishment of cell polarity and the regulation of polymerization of actin (major component of the cytoskeleton of the hair Cells) is related to the role in hearing impairment [30].

KCNQ4 – DFNA2

Mutation in this gene affect potassium channels also present in the cochlea of mammalian provoke an alteration of the ion recycling into the endolymph at the level of the basolateral membrane of the outer hair cells.

Consequently, *KCNQ4* gene mutation causes a progressive hearing loss more prominent in high frequencies [31].

GJB2 (Connexin 26) – DFNA3

Whereas the *GJB2* gene is the major gene responsible for non-syndromic, recessive deafness, there is some controversy as to the role of *GJB2* in dominant deafness (DFNA3).

Autosomal-dominant hearing loss shows a different phenotype, consisting of pre-lingual to late-childhood onset, mild to profound, progressive hearing loss [32].

Mutations in the *GJB2* gene are also responsible for autosomal-dominant syndrome with keratoderma and sensorineural deafness (Vohwinkel syndrome) and other forms of autosomal-dominant palmoplantar keratoderma with deafness [33].

TECTA (a-Tectorin) – DFNA8/DFNA12

TECTA gene encoding a non-collagenous component of the tectorial membrane in the inner ear (a-tectorin). Mutations of this gene disrupt the structure of the tectorial membrane, leading to inefficient transmission of sound to the mechanosensitive stereociliary bundles of the hair cells [34].

The hearing loss was congenital, non-progressive, moderate to severe, involved mainly the middle frequencies.

EYA4 – DFNA10

EYA4 is part of family transcriptional activators protein (*EYA1-4*) that facilitate normal embryonic development. Mutation in *EYA1* causes BOR (Brachio-Oto-Renal) syndrome whereas mutation in *EYA4* causes isolated hearing loss.

Deafness is progressive, moderate to profound and bilateral [35].

WFS1 – DFNA 6/14/38

WFS1 encodes a transmembrane protein (wolframin) the function of which is currently unknown.

In the most part of the cases, mutation in WFS1 is responsible for Wolfram syndrome but can be, also, a cause of non-syndromic low-frequency sensorineural hearing loss.

In this non syndromic case deafness is characterized by slowly progressive, low-frequency (<2000 Hz) sensorineural hearing loss [36].

SYNDROMIC CHL

Syndromic CHL_Autosomal Recessive Hearing Loss

Usher Syndrome

Usher syndrome prevalence ranging from 1/6000 to 1/10000 and it represent the 3-5% of infant hearing loss.

It is characterised by bilateral hearing loss and visual deficiency (until the blindness).

There are three subtypes based on severity of the deafness, vestibular dysfunction and the onset of visual impairment: USH1, USH2 and USH3.

Visual deficiency is due to retinitis pigmentosa: a gradual retinal degeneration leading to decreased night vision, loss of peripheral vision, and blindness.

In USH1 subtype can be found severe to profound congenital hearing loss, congenital vestibular dysfunction and progressive to severe blindness (started with might blindness in childhood).

Table 3. Genes associated with Usher syndrome subtypes

Subtype	Genes	Protein	Protein Function
USH1B	MYO7A	Myosin VIIA	Actin-based motor protein
USH1C	USH1C	Harmonin	scaffold protein
USH1D	CDH23	Cadherin23	Cell adhesion
USH1F	PCDH15	Protocadherin 15	Cell adhesion
USH1G	USH1G	SANS	Scaffold protein
USH1J	CIB2	CIB2	Calcium and integrin binding protein 2
USH2A	USH2A	usherin	Cell adhesion
USH2C	GPR98	VLGR1	Adhesion G protein-couple receptor VI
USH2D	DFNB31	whirlin	scaffold protein
USH3A	CLRN1	Clarin1	Auxiliary subunit of ion channels

USH2 patients have moderate to severe CHL, no vestibular dysfunction and retinitis pigmentosa started between the age 10 to 40.

In the USH3 subtype there are progressive hearing loss, variable vestibular dysfunction and retinitis pigmentosa started from the age of 20.

The gene and loci associated with Usher syndrome is show in Table 3 [37].

Pendred Syndrome

Prevalence of Pendred syndrome is 7.5/100.000 newborns.

Pendred syndrome comprises a phenotypic spectrum of sensorineural hearing loss (SNHL), vestibular dysfunction and abnormal iodine metabolism.

SNHL is usually bilateral, progressive, from mild to profound degree and can be congenital or with a later onset.

Frequently there are associated temporal bone abnormalities (enlarged vestibular aqueduct with or without cochlear hypoplasia).

Abnormal iodine metabolism develop euthyroid goiter sometimes detected at birth, but often not clinically evident until 8 years of age. Often this patient have thyroid dysfunction, ranging from euthyroid to hypothyroidism.

In at least 50% of patients with Pendred syndrome, the molecular diagnosis is established by identification of biallelic pathogenic variants in SLC26A4 or double heterozygosity for one pathogenic variant in SLC26A4 and one pathogenic variant in either FOXI1 or KCNJ10 [38, 39].

Jervell and Lange-Nielsen Syndrome

It is estimate that prevalence of Jervell and Lange-Nielsen syndrome is 1.6 to 6 per 1.000.000 people worldwide.

This syndrome is characterized by severe-profound hearing loss, prolongation of the QT interval at basal ECG and sometimes T-waves abnormalities, and by an increased susceptibility to life-threatening ventricular arrhythmias.

KCNQ1, KCNE1 are the gene associated with the syndrome and they encode potassium channels found in the stria vascularis of the cochlea and in the heart [40].

Wolfram Syndrome

This syndrome is characterized by diabetes mellitus, diabetes insipidus, optic atrophy and deafness.

Often there are progressive neurologic abnormalities (cerebellar ataxia, peripheral neuropathy, dementia, psychiatric illness, and urinary tract atony), and other endocrine abnormalities

Sensorineural hearing loss is slow progressive emerging in late childhood. Median age at death is 30 years [41].

Pompe Disease

Pompe disease is a rare multi-systemic metabolic myopathy associated at conductive or sensorineural hearing loss in almost 50% of the cases.

This syndrome is caused by autosomal recessive mutations in the acidic alpha glucosidase (GAA) gene [42].

Syndromic CHL_Autosomal Dominant Hearing Loss

Waardenburg Syndrome

Prevalence of the Waardenburg syndrome is 1/42.000 and it represents 2-5% of infant hearing loss.

This syndrome is characterized by sensorineural hearing loss, abnormal pigmentation of the skin and hair, dystopia canthorum, heterochromia iridis and pinched nose.

There are four subtypes based on the presence or absence of the additional symptoms: WS1, WS2, WS3 and WS4.

WS1 and WS2 are the most frequent and WS1 is characterized by dystopia canthorum, wide-set eyes. WS3 is characterized by dystopia canthorum and musculoskeletal abnormalities of the upper limbs whereas WS4 is associated with Hirschprung diseases.

Gene involved in WS1 is PAX3 and MITF in WS2, these genes are involved in the regulation of melanocyte [43].

Brachio-Oto-Renal Syndrome

Brachio-Oto-Renal (BOR) syndrome is characterized by sensorineural or conductive hearing loss, cup-shaped pinnae, preauricular pits, branchial cleft fistulae and bilateral renal anomalies.

Prevalence of this disease is 1/40.000 and it is 2% of infant hearing loss [44].

Stickler Syndrome

Stickler syndrome is characterized by progressive sensorineural hearing loss with cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis; myopathy, retinal detachment and vitreoretinal degeneration (only in Types 1 and 3).

The prevalence is about 7/7.500 to 1/9.000 newborns.

There are five subtypes based on the collagene gene involved: in type I COL2A1 is involved, COL11A1 in Type II and COL11A2 in Type III. Types IV and V are transmitted in recessive autosomal manner [45].

Treacher Collins Syndrome

Treacher Collins syndrome is characterized by microtia and malformed ears, midface hypoplasia, downslanting palpebral fissures, coloboma of outer 1/3 of lower eyelids, and micrognathia.

TCOF1, POLR1C and POLR1D are the three genes associated to this syndrome [46].

Syndromic CHL_X-Linked Hearing Loss

Alport Syndrome

Alport syndrome is characterized by progressive sensorineural hearing loss, renal disorders (glomerulonephritis, haematuria (and renal failure) and ocular abnormalities.

COL4A3, COL4A4 and COL4A5 are the three genes associated with Alport syndrome. All encoding for a collagen protein [47].

CONCLUSION

A genetic diagnosis for congenital hearing loss is required for different reasons, in particular for choosing appropriate therapeutic options, for treating associated medical problem (syndromic forms) and for predicting the progression of the degree [48].

New treatments and screening strategies are available for identifying the responsive gene, e.g., Next Generation DNA sequencing that allows the simultaneous analysis of a large number of genes causing CHL with a higher probability of gene identification.

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Chapter 56

NEUROPLASTICITY AND SENSORINEURAL HEARING LOSS

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ABSTRACT

Neuroplasticity is the ability of central nervous system to modify his own functions based on changes of external or internal factors, and it's the basis for numerous physiologic and pathologic events in otology. Sensorineural hearing loss implies a cochlear deficit but also modifications from acoustic tract up to auditory cortex. It determines morphofunctional changes, through neuroplasticity, that may be influenced by cochlear implants and hearing aids. There are many trials that shown a remarkable hearing development in deaf infant after cochlear implant or usage of hearing aids. However, many questions remain around the right time to act, due to the greatest neuronal response in younger children. Animal experimentation has shown also tonotopic changes in cortical and subcortical areas after cochlear lesions, that depends upon age and damage extension, as neuronal reorganization differ from neonatal and adults. In this chapter we'll discuss about central neuronal network modifications, after sensorineural hearing loss, emphasizing clinical consequences, in particular the usefulness of early diagnosis and rapid treatment.

Keywords: neural plasticity, hearing loss, deafness, neuroplasticity, brain

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INTRODUCTION TO NEUROPLASTICITY

Since Rita Levi Montalcini's studies on anatomic changes to auditory pathways after experimental lesions of chick embryo, neuroplasticity has been widely recognized, and with that neuronal capacity to change itself in reaction to stimuli and lesions (Levi-Montalcini 1949). Mechanisms of neural plasticity have been the focus of interest in research for many decades. Plasticity is based in part on changes in synaptic function (synaptic plasticity), on change in synchronization in the neuronal networks, and on change in inter-neuronal connection patterns within neuronal networks (Thomas et al., 2018, Martinez et al., 2015).

This may be associated on synaptic strengthening as postulated by Hebb's studies. Exactly as he said "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased. The synaptic strengthen works through changes in pre-synaptic and postsynaptic areas. It could work on augmented release probability of neurotransmitters, incremented number of release sites or vesicles in the pre-synaptic neuron, while on receptor sensitivity and quantity of elicitable receptors in the post-synaptic neuron (Wang, Ko, and Kelly 1997).

This phenomenon may also explain the way of *Central Nervous System (CNS)* development, through the repeated stimulation of genetically determined neural pathway that leads improvement and development of some functions. A neuron is linked to many different other neurons but is activated just by some.

Neuroplasticity may explain the phantom limb's etiology or in auditory area, tinnitus's etiology. Certain types of tinnitus could arise from auditory neurons that somehow develop self-perpetuating activity. With our understanding that the brain is full of networks it is easy to conceive of local circuits being reinforced to the point of reverberation that in the auditory cortex may determine tinnitus (Eggermont 2012). Also the vestibular compensation after an issue involving one of the vestibular organs should be related to the neural plasticity (Lorusso et al., 2017, Dispenza et al., 2015, Dispenza, Kulamarva, and De Stefano 2012, Dispenza and De Stefano 2012, Dispenza et al., 2011).

Neuroplasticity is heavily studied on its variability during lifespan. The capacity for reorganization of the brain is more extensive during development. Especially in neonatal age comes a gargantuan synaptogenesis that last until the five years of age, followed by a dendritic pruning. Therefore comes the children ability to learn and grow at wonderful speed. An explanation may be that, in developing animals, due to immaturity of neuronal membranes and ionic channels, cortical postsynaptic potentials are known to have a longer duration. This has the effect of naturally boosting synaptic plasticity, as individual postsynaptic potentials can more easily temporally overlap. Temporal summation can by that cause a strong depolarization of postsynaptic cells. The eventual consequence of this effect is higher plasticity during early development. This phenomenon has a clinical effect, since most aspects of learning and intellectual functions may be acquired only in earlier age.

NEUROPLASTICITY IN THE AUDITORY SYSTEM

The neuroplasticity of the auditory system was object of study of expert otologists all over the world, in order to understand the mechanism and the relationship with different area

of CNS (Dispenza et al., 2011, De Stefano et al., 2011, De Stefano, Kulamarva, and Dispenza 2012).

It has been shown that a pre-lingual sensorineural hearing loss may cause cognitive and relational developmental deficits; while in adults the development of an auditory deficit is associated with dementia and decreased attention (Contrera et al., 2017, Salvago et al., 2017). Alterations of cerebral white and gray matter have been reported in patients with hearing loss (Yang et al., 2014). Focal deficits of the white matter of the superior temporal gyrus for deaf children in prelingual age and volumetric decreases in gray matter in areas adjacent to the auditory cortex in individuals with bilateral hearing loss were demonstrated (Husain et al., 2011). Yang compared T1 weighted sequences and task free fMRIs of 14 adult patients with hearing impairments of moderate severity and 19 controls: Voxel based morphometry (VBM) showed decreased gray matter volume in bilateral posterior cingulate, lingual and the amplitude of low frequency fluctuation, calculated to analyze brain activity, was decreased in bilateral precuneus, left inferior parietal lobule, right inferior frontal gyrus and insula, and increased in right inferior and middle temporal gyrus (Figure 1) (Yang et al., 2014).

Boyen also applied VBM analyses to MRIs of normal-hearing control subjects, hearing-impaired subjects without tinnitus and hearing-impaired subjects with tinnitus. The two hearing impaired groups had well matched audiograms for frequencies of 8 kHz. VBM analyses revealed that both hearing impaired groups, compared to healthy controls, had GM volume increased in the superior and middle temporal gyrus and limbic areas and decreased in the superior frontal gyrus, frontal areas, occipital lobe and hypothalamus (Boyen et al., 2013).

Increased amplitude of low frequency fluctuation may determine a neuroplastic change in response to hearing loss. Many reviews showed that hearing loss brain adapt through unimodal and cross-modal plasticity (Kral 2007).

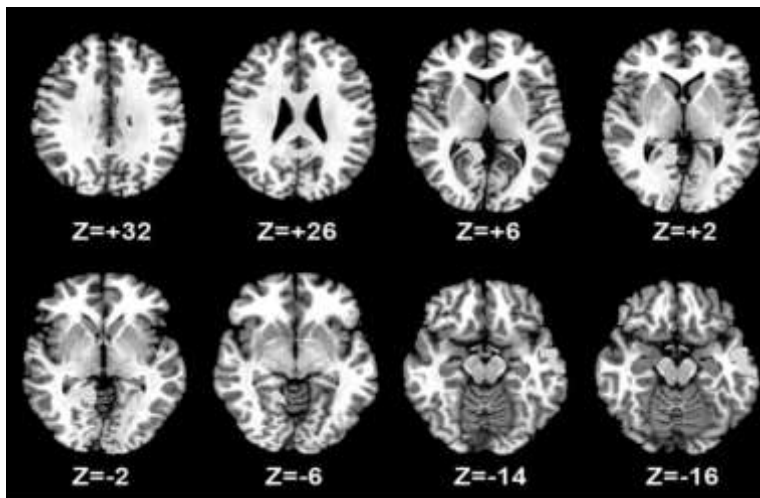


Figure 1. Brain areas with decreased gray matter. Modified from: Yang et al., *Hearing Research* 316 (2014) 37-43.

UNIMODAL PLASTICITY

Unimodal plasticity is the capacity of changing the neuronal pathway inside a single area; in the auditory area it mostly deal with tonotopic modifications and relations between primary auditory cortex and higher order cortex. It's a good idea to propose Merzenich studies on deaf cats.

An experiment studied cats treated shortly after birth with the ototoxic aminoglycoside amikacin, which resulted in a basal cochlear hair cells lesion. Though ABR evaluations it was assessed that the stimuli for low frequency sounds could still be transmitted, but it was gone for high frequency sound. Over time, auditory cortex showed normal representation of low frequencies, but the cortical region deprived of normal input by the partial cochlear deaf-ferentation now contains neurons that are all tuned to 6 to 8 kHz. Thus there was an abnormally overrepresentation of the still captable frequency in the auditory cortex. Also, one of these subjects however showed an injury both on basal and apical cochlea. This kitten also developed a cortical frequency map in which there was a very large iso-frequency area where all neurons have a common 6.6-kHz frequency tuning (Kaas, Merzenich, and Killackey 1983).

Qualitatively, similar results are also found at the cortical level if the lesions are made in an adult animal, as showed by Robertson and Irvine studies and many others. At the level of the auditory cortex, after cochlear lesions were induced in the adult animal, the pattern of reorganization of tonotopic maps was similar to that of the developing neonate (Rajan and Irvine 1998). However, intuitively, considerable differences should be expected in the extent of the cortical tonotopic map reorganization in subjects with lesions made in early development compared with those made in adulthood since the importance of early sensory stimulation in driving the development of the mature brain has already been discussed. In fact, if we study the subcortical reorganization in adult and developmental animals many differences may be exposed.

It was showed that determining a cochlear lesion in a developmental animals lead to subcortical modifications along the auditory brain steam, with a tonotopic map reorganization, at inferiors colliculi and thalamo particularly, in large part reflecting what occurs at cortical level. Such subcortical reorganization apparently does not occur for similar lesions made in the adult. The age of induction of hearing loss, neonatal, childhood or adult does not appear to affect the outcome; increased spontaneous ring rates, increased neural synchrony and reorganization of the cortical tonotopic map (Harrison 2001).

Therefore neonatal induced hearing loss also results in reorganization of the tonotopic map in the inferior colliculus, which does not occur after adult acquired hearing loss (Eggermont 2017).

Dealing with neural pathway modifications between higher order auditory cortex and primary auditory cortex, we should remember that higher order auditory cortex maturity come necessarily from long term hearing experience, especially in developmental subject. We can expose Sharma's studies on prelingual deaf children. It showed in early implanted deaf children an increasing amplitude and decreasing latency of wave P1 and an appearance of wave N1 with cochlear implant stimulation, whereas late-implanted children, especially those implanted in late teens, do not develop wave N1. Since N1 wave is generated in the higher order cortex we can assume that without auditory stimuli in early age, those areas doesn't

develop and become significantly compromised (Sharma et al., 2002). Also, higher order cortex tends to reorganize cross-modally, leading to interaction with visual, and possibly others areas, in an attempt to compensate through visual and other stimuli to the auditory deficit.

CROSS-MODAL PLASTICITY

Cross modal plasticity works with connections between different areas. In Bertrand and Sharma studies, it was proved an higher order auditory cortex activation in response to a radial modulated visual grating stimulus giving the effect of apparent motion, in prelingual deaf children with cochlear implants, using CVEP. While normally hearing children show cortical activation of areas typically associated with visual procession, while the CI children demonstrated additional activation of right lateral temporal cortex for the higher order N1 and P2 CVEP components (e.g., right inferior, middle, and superior temporal gyrus). Furthermore, speech perception performance in background noise using a clinical test (BKB SIN) was significantly negatively correlated with CVEP latency for CI children, such that poorer speech perception was associated with earlier CVEP N1 latency. However, it appears that auditory reactivity is maintained despite cross-modal re-organization by vision (Bertrand et al., 2012).

Sandamn showed that even in adult crossmodal plasticity happens as well, since its studies showed an increased activation in the auditory cortex during CVEP, in both prelingually and postlingually deaf adults compared to the normal hearing group. Also increased CVEP amplitude over temporal cortex is associated with poor speech perception in quiet and noise environment (Chen et al., 2016).

Currently it is not well defined how long it takes to develop cross-modal plasticity in adults. A case report study showed a visual activation of auditory cortex at least three months after sudden hearing loss, which increased over time, up to increasing its efficiency up to one year. Interestingly, there was a positive association between N1 amplitude at CVEP and speech perception. These findings are from a single case study and they should be interpreted cautiously (Glick and Sharma 2017).

Another area related to higher order cortex of deaf patients in cross modal plasticity it's the post-central gyrus of somatosensory cortex. As in, numerous studies showed a simultaneous activation of both somatosensory and auditory area cortical during cortical somatosensory evoked potentials (CSSEP) and, when treated with cochlear implants, even in cortical auditory evoked potentials (CAEP) In this case, findings of cross modal plasticity are related to poor speech perception performance as well (Cardon and Sharma 2018).

Even if visual cortex may be recruited by higher order auditory cortex, to evolve speech and communication by other mean than auditory input in hearing loss, many doubts remain over usefulness of somatosensory recruitment and many authors suggest this may happen, instead of a functional modification, due to close proximity of somatosensory and auditory cortices and the overlapping of somatosensory and auditory neurons subcortically, as a result of hearing impairment (Glick and Sharma 2017).

Cross modal plasticity take part also in relations to contralateral auditory cortex as in Khosla et al., study, especially in unilateral hearing loss (Khosla et al., 2003).

Normal-hearing subjects show significant latency and amplitude differences between ipsilateral and contralateral peaks for all components of the CAEP, with contralateral source activities that were typically larger and peaked earlier than the ipsilateral activities. However, in unilateral hearing loss, the patients showed a reduction of both amplitude and latency differences, when the best hearing ear was stimulated. Thus, unilateral hearing loss leads to a more synchronous and symmetrical activation of the auditory cortex (Eggermont 2017).

All this studies showed the higher order auditory cortex is the main protagonist of cross-modal plasticity as it's the one to get in relation both with visual and somatosensory auditory cortex, but also with frontal area and contralateral auditory area. It takes parts in language development and speech perception, it's heavily binded to the auditory input in normal people, even if it's relation with the visual and other area it's already proved by McGurk effect. However in absence of hearing experiece, the representation between higher order cortex and primary order cortex remain to a rudimentary level, and the higher order cortex due to their strong inputs also from nonauditory areas, take-over new functions and undergo crossmodal reorganization.

NEUROPLASTICITY AND COCHLEAR IMPLANTS

Cochlear implants are surgically implanted hearing aids used on patients with severe to profound sensorineural hearing loss in both ears to provides a sense of sound. In cochlear implants, cochlear transduction pass through a microphone then comes the spectral analysis through a bank of bandpass filters within a speech processor. At the very end, the output of each bandpass filter is directed to one for up 24 intra-cochlear electrodes positioned to stimulate auditory nerve fibers at tonotopically appropriate position along the cochlear spiral.

Electrical stimulation of the auditory nerve by cochlear implants evokes a pattern of activity, which differs from that evoked by acoustical stimulation in the normal ear. The spread of activation in the auditory nerve is much larger with electrical stimulation than with acoustical stimulation (Middlebrooks, Bierer, and Snyder 2005). Even the most focused stimulation strategies, as with the tripolar electrode configuration (Kral et al., 2002), do not come close to the acoustical stimulation and, in addition, are not favorable in cases of patchy degeneration of the auditory nerve. Moreover, randomness in the temporal firing pattern with electrical stimulation is much less than it is in the normally activated auditory nerve partially due to the loss of spontaneous activity in “deaf” auditory nerve fibers. Electrical stimulation at a high rate such as used in modern cochlear implants might induce a slight increase in randomness of the firing patterns because of refractory periods and sub-threshold electrical stimulation. Last but not last, simultaneous activation of several electrodes can lead to unwanted current flows between the active electrodes. Therefore, interleaved stimulation is used, which further biases the temporal excitation pattern when compared to natural acoustic-evoked activity.

Thus, after cochlear implantation, most of the representations of sounds in the nervous system have to be rebuilt to fit the characteristics of the new coding of auditory input.

Without auditory brainstem lesions, the outcome of cochlear implantation depends heavily on central factors, that is, its functional status and its plasticity (Kral and Tillein 2006).

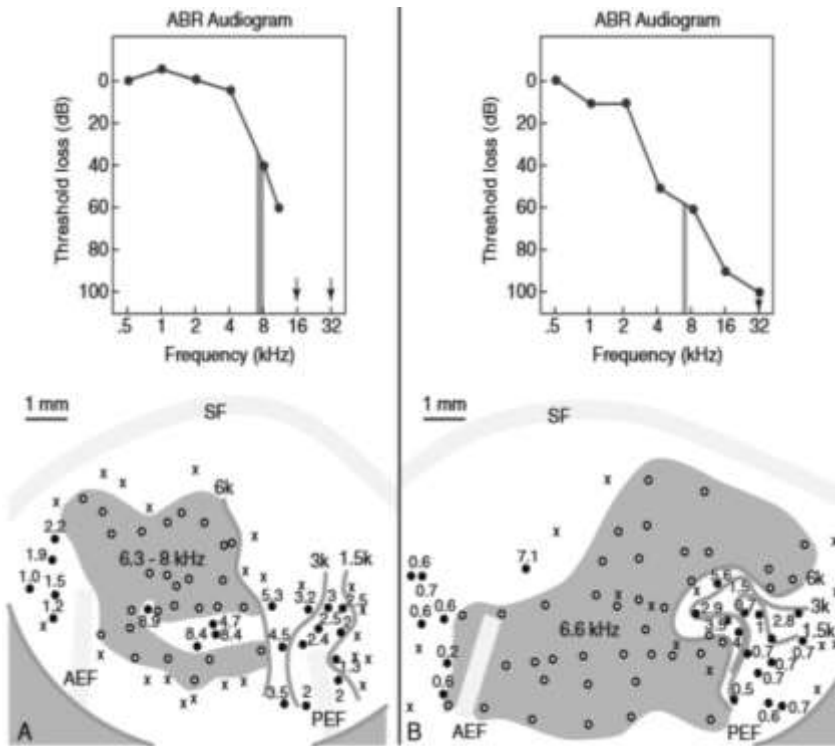


Figure 2. Cortical tonotopic maps that developed in two cats with neonatal basal cochlear lesions. Kittens were treated with the ototoxic aminoglycoside amikacin to produce basal lesions to the cochlea, the effects of which are reflected in the auditory brainstem response (ABR)–derived audiograms (upper panels). A, In this subject, the cochlear lesion was confined to the basal region. B, In this subject, hair cell damage was maximal at the cochlear base, but scattered hair cell loss extended up to apical regions. Shading indicates regions in which all neurons have similar tuning properties. AEF, anterior ectosylvian fissure; PEF, posterior ectosylvian fissure; SF, sylvian fissure (Modified from: Cumming's *Otolaryngology, Head and Neck Surgery*, sixth edition, chapter 132 "Neural Plasticity in Otology: 2042).

Many speculations were born about effects of cross modal plasticity in hearing recovery. Lee's studies have shown that delayed hearing-aided subjects presented the signs of cross-modal plasticity, and were less responsive to cochlear implant with greater difficulty in learning language and speech; the subjects who received an early prosthesis were often free of signs of cross-modal plasticity and responded better.

These studies, however, had the defect of referring to the difference in timing of prosthesis, for which an ulterior study was performed on adult subjects suffering from post-lingual deafness and it was highlighted how the subjects with activation of the auditory cortex at CVER responded poorly to the hearing aids (Lee et al., 2001). Therefore it is possible to speculate that signs of cross modal plasticity can be exploited to evaluate the expectation of response to the cochlear implant. However, another study plasticity showed that cochlear implantation progressively regressed to a response only of the visual cortex in response to VCER.

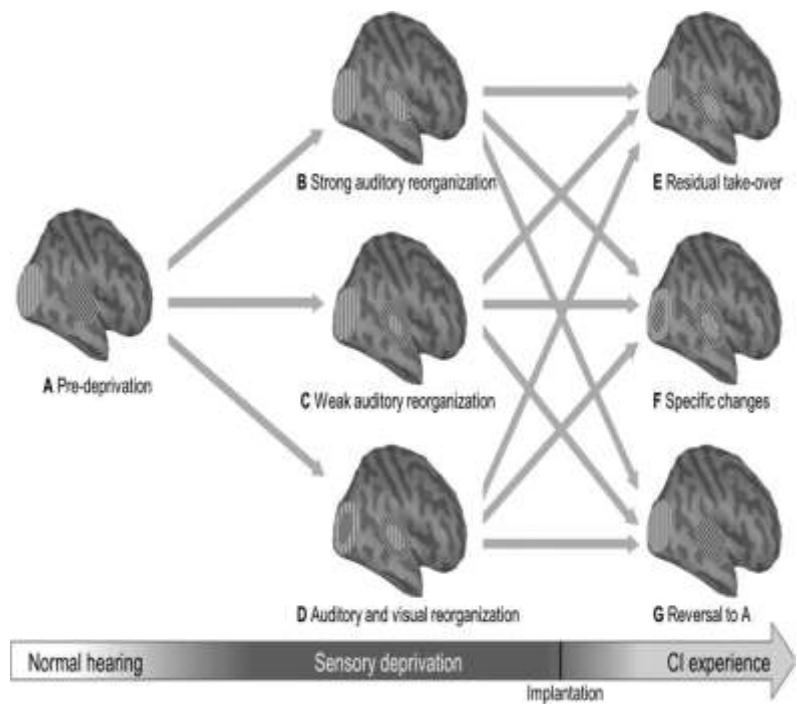


Figure 3. Schematic sketch illustrating cortical reorganization patterns resulting from sensory deprivation and hearing restoration with a CI. “Cortical reorganization in postlingually deaf cochlear implant users: intra-modal and cross-modal considerations.” Modified from: Stropahl et al., *Hearing Research*, Elsevier, 343(2017): 128-137.

Therefore, the concept remains that cross-modal plasticity is an adaptive response to deafness, which acts by potentiating the functioning sensory cortex areas and of the frontal cortex for TOP-BOTTOM response mechanisms to compensate for the auditory deficit. It is possible that in some subjects this phenomenon happens so well that even after prosthetics there is no recovery of the normal function of the auditory cortex, while, paradoxically, those who do not effectively highlight spoken language. The results discussed above have relevance for decisions regarding cochlear implants in congenitally deaf children (Kral and Tillein 2006). One question that has often been asked is whether the caretakers of children with cochlear implants should keep signing with these children, or if this would be counterproductive for learning and maintaining a language through spoken words using the cochlear implant? Arguments for both alternatives have been made. Signs accompanying spoken language might facilitate learning by appropriately activating the semantic auditory system with the associative language networks already established in the brain. On the other hand, signing might prevent the reassignment of high order auditory cortex to the auditory modality, and thus it may counterproductive in learning spoken language.

CONCLUSION

In this chapter we have evidenced how neuroplasticity plays a very important role in the regulation of cortical neuronal networks in response to inputs of various kinds, and in

different age. In the case of deafness in the prelingual period, an early prosthetic implant allows the development of normal and physiological neuronal networks at the level of primary auditory cortex and higher order, as well as between areas, and promotes the stimulation that the central nervous system needs for development. Otherwise, in working between the different areas, in attempt to compensate for function, this can lead to a disadvantage in normal recovery after hearing aids.

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Chapter 57

NEURORADIOLOGY OF THE HEARING SYSTEM

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ABSTRACT

Hearing loss is one of the most frequent indications for CT and MR examinations of the auditory system. Such a symptomatology is becoming increasingly common in today's society and is extremely disturbing for patients. Causes may involve the auditory pathway at any level.

In most cases, neuroradiological examinations represents a mandatory step, within a multidisciplinary workup, towards final diagnosis, therapeutic plan and subsequent follow-ups. This chapter will introduce this critical topic starting from an imaging-based exposition of the anatomy and function of the auditory system. The chapter will include some hints on the choice of the best imaging examination to perform on each patient since the type of hearing loss determines which imaging study will yield the most diagnostic information. Practical coverage of the neuroradiological findings in conductive, sensorineural and mixed hearing loss forms will be presented. Ranging from congenital to acute and chronic causes, from children to adults, the role of imaging-based examinations will be illustrated for both common and uncommon diseases of the hearing system.

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To increase reading and review experience, the authors will include concise descriptions (in a bullet outline format and/or in tables) of all the discussed key information related to anatomy, function and pathology. High-quality CT and MR images will support the reader in each paragraph for an optimal learning experience of the discussed topics.

1. INTRODUCTION TO THE ROLE OF IMAGING

Imaging techniques have historically supported the study of the auditory system which always required dedicated and optimized protocols to ensure a good visualization of its peculiar anatomy and related pathology.

Nowadays, Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) are the most used imaging modalities to investigate the auditory pathway at any level.

Conversely, the role of plain film radiographs has been significantly reduced and limited to specific applications over the past years (i.e.: Stenvers' projection is still routinely used for intra- and/or postoperative evaluation of a cochlear implant lead).

Digital subtraction angiography (DSA) is still used in cases of hypervascular masses and vascular malformations involving the temporal bone or the auditory pathway.

Diagnostic ultrasounds found little use in this context if not for the evaluation of periauricular lesions or ultrasound-guided biopsies.

Nuclear medicine modalities, such as Positron Emission Tomography (PET) may be used for the assessment of temporal bone masses and/or nodal metastases.

Last but not least, dedicated devices such as cone beam CT (CBCT) that are more recently spreading worldwide, deserve mention since they have been successfully used for middle ear diseases [1], cochlear implants [2-4], cholesteatoma surgery [5-6], guidance of temporal bone surgery [7] and other specific pathologies such as otosclerosis [8-9].

CBCT equipment uses a rotating gantry on which an x-ray tube and a reciprocating solid state flat panel detector is attached [10]. This allows the operator to acquire a full dataset of the region of interest with a single 180-360° rotation of the gantry (scanning time varies from nearly 5 - using pulsed scans - to about 40 seconds). Because of their high spatial resolution (slice thickness could be in the order of some tens of microns), lower radiation dose, lower sensitivity to metallic and beam hardening artifacts and their reduced costs, these scanners have triggered a lively interest in the scientific community. Furthermore, the production of compact CBCT scanners enabled their usage in an office-based setting [10]. On the other hand, if compared to conventional CT, CBCT images are noisier because of the large volume being irradiated, are more sensitive to movement and distortion artifacts, partial volume averaging, undersampling and cone-beam effect. Last but not least, CBCT have a poor soft tissue contrast and their usage is substantially limited to oral and maxillofacial radiology [11].

1.1. Computerized Tomography (CT) Study Protocol

CT is the primary imaging modality for evaluating the osseous components of the temporal bone region [12-13]. The increasing number of multi-detector CT (MDCT) installations has been followed by the wide adoption of helical study protocols dedicated to

high resolution temporal bone imaging. Nowadays, thanks to MDCT scanners, it is no longer necessary to ask patients to lay on the gantry in uncomfortable positions to obtain optimal study planes as we used to do in the past years with single-row-detector CT equipment using sequential study protocols. MDCT protocols (see Table 1) for temporal bone region are based on sub-millimetric (slice thickness should never exceed 1.0 mm), usually isotropic datasets and related multiplanar reconstructions (MPR). All temporal bone studies should be reconstructed using a bone algorithm and each side should be separately reconstructed using a magnified small field of view (FOV) for both axial and coronal planes. Reconstruction of the posterior fossa using soft-tissue algorithm with a wider FOV is recommended.

Table 1. Example of standard protocols for a 16 detector rows scanner (GE Brightspeed 16).

Acquisition parameters (helical scan type)	Protocol		
	<2y	>2y	Adults
Tube voltage (kV)	120	120	140
Tube current (mAs)	200	200	260
Axial thickness (mm)	0.625	0.625	0.625
Scan type	Helical full (0,7s)	Helical full (1s)	Helical full (1s)
Pitch	0.562:1	0.562:1	0.562:1
Speed (mm/rot)	5.62	5.62	5.62
Beam collimation (mm)	10	10	10
Interval (mm)	0.625	0.625	0.310
SFOV (cm)	10	10	24
DFOV (cm)	6	6	10
Scan durations (s)	11.44	16.33	9.3
N° of images	129	129	130
Matrix size	512 x 512	512 x 512	512 x 512
Maximum estimated CTDI _{vol} (mGy)	52.04	74.34	143.70
DLP (mGy-cm)	478.21	682.93	750.09
Reconstruction kernel (window width/level)	Bone Plus - GE's hard/sharp kernel (4095/600)		

SFOV: Scan field of view; DFOV: Display field of view; CTDI_{vol}: computed tomography dose index; DLP: dose-length product

If a MDCT scanner is not available (or if reformatted coronals from the axial scans are not possible/adequate), direct coronal images should be considered. To ensure a direct coronal plane, the patient is asked to lay in the prone position with the head tilted back (for patients who cannot tolerate this position, supine positioning with a pillow under the shoulders and the head tilted posteriorly should be tried). For direct coronal plane imaging, the gantry should be perpendicular to the infraorbital-meatal line. The typical planning should be from the level of the posterior temporo-mandibular joint anteriorly, through the entire mastoid air cells posteriorly.

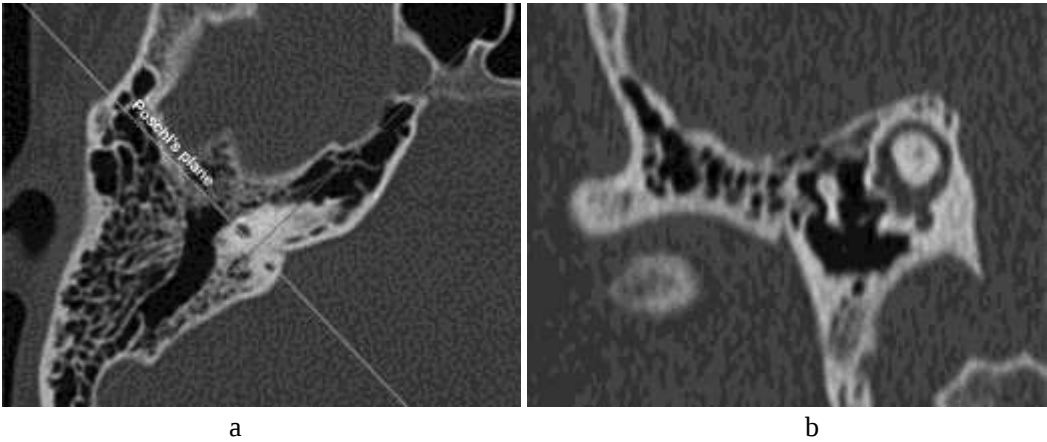


Figure 1. a) Axial CT passing through the superior semicircular canal (SSCC) with superimposed DICOM references lines for a MultiPlanar Reconstruction (MPR) among Poschl's plane obtained by tilting the MPR plane parallel to the SSCC; b) the whole SSCC is fully exposed on the obtained MPR.

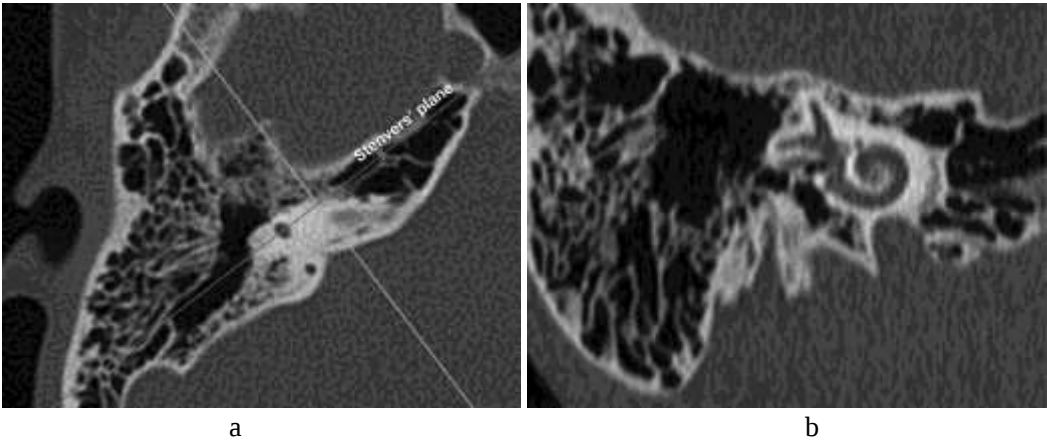


Figure 2. a) Axial CT passing through the superior semicircular canal (SSCC) with superimposed DICOM references lines for a MultiPlanar Reconstruction (MPR) among Stenvers' plane obtained by tilting the MPR plane perpendicular to the SSCC; b) the cochlea is exposed from basal turn to apex on the resulting MPR plane.

If a MDCT scanner is available, high resolution temporal bone imaging is obtained with the patient placed supine and the head in a neutral position. The gantry of the scanner should be angled parallel to the infraorbital-meatal line. Two topograms (one in the anterior-posterior projection and one lateral) are usually scanned to plan the study ensuring the full coverage of the region of interest. The typical axial planning should start from the arcuate eminence superiorly and the mastoid tip inferiorly. The excursion of the scan is planned to avoid including the eyes in the pathway of the x-ray beam to reduce the radiation dose to the lens. Coronal MPRs are usually obtained tilting the plane perpendicular to the infraorbital-meatal line. Considering the three-dimensional (3D) nature of the scanned dataset additional reformations, with no compromises in terms of image spatial resolution, are possible and could result in being very useful in specific cases. For example, if a superior semicircular canal dehiscence is suspected, Poschl plane (Figure 1) among the short temporal bone axis

(obtained by tilting the MPR plane parallel to the superior semicircular canal) should be considered [14]. Similarly, Stenvers' plane (Figure 2) among the long temporal bone axis (obtained by tilting the MPR plane perpendicular to the superior semicircular canals) should be considered to evaluate a cochlear implant lead [15].

Intravenous (i.v.) administration of contrast medium is usually not indicated for temporal bone imaging but may be helpful when evaluating patients with acute mastoiditis in order to evaluate adjacent vascular structures such as the transverse sinus, to investigate the involvement of the mastoid and/or the perimastoid dissemination of a disease, or if a temporal bone tumor is suspected.

1.2. Magnetic Resonance Imaging (MRI) Study Protocol

MRI is the primary imaging modality for evaluating the non-osseous components of the temporal bone region [16-17]. A high field strength MRI scanner ($\geq 1.5T$) is typically used together with a phased array head coil (8-, 16- or 32-channels). The use of dedicated surface coils can improve the signal/noise ratio at the cost of a lower depth and reduced FOV. MRI is the first imaging examination requested in case of suspected retrocochlear pathology and cranial nerve dysfunction. One of the most common indications for an MRI examination of the temporal bone is sensorineural hearing loss [18-19]. MRI is also useful in patients with CT-defined infections or neoplasms to determine if there is an involvement of the intracranial compartment.

Even if MDCT is still the preferred modality if a labyrinthine or cochlear lesion is suspected or in patients with subjective pulsatile tinnitus, there are specific lesions (such as cochlear schwannomas or labyrinthine hemorrhages) and cases (such as patients with objective pulsatile tinnitus - audible bruit) that could be better detected and studied by MRI.

During the MRI examination, the patient lays in the supine head-first position. A fast (low resolution) T2-weighted three plane localizer is scanned. Axial sequences are planned parallel to the line passing through both internal auditory channels (IACs) and perpendicular to the brain stem; the number of slices must be sufficient to cover the ROI from the hippocampus up to the line of the first cervical vertebral body. Coronal sequences are planned parallel to the line passing through both internal auditory channels (IACs) on the coronal plane and parallel to the brain stem on the sagittal plane. The number of slices must be sufficient to cover the ROI from the posterior border of sphenoid sinus up to the fourth ventricle anterior wall. An example of an MRI protocol for the evaluation of the temporal bone is reported in Table 2; to ensure a good visualization of the peculiar anatomy and related pathology of this region a small FOV is used and slice thickness should not exceed 3 mm with no interslice gap. Axial and coronal T1-weighted pulse sequences acquired before and after administration of i.v. contrast agent should be included (at least one post-contrast T1-weighted sequence with fat saturation should be scanned as well). Nowadays, thin section 3D constructive interference in steady-state (3D-CISS) T2-weighted sequences are mandatory [20]. This technique has different names for each vendor: fast imaging, employing steady-state acquisition (FIESTA) by GE, true fast imaging with steady-state precession (FISP) by

Table 2. Example of standard protocols for 1.5T scanners using a dedicated 8-channel phased-array head coil

Parameters	MRI scanner: 1.5T Philips Achieva / 1.5T GE HDxT					
Pulse sequence	2D Ax T1w TSE / FSE	2D Ax and Cor T2w TSE SPIR / FSE FAT SAT	3D Ax B-FFE / FIESTA	2D Cor DWI / Ax DWI PROPELLER (b=0/1000m/s ²)	2D Ax T1w (Gd) SE	3D AX (Gd) FFE SPIR / SPGR FAT SAT
FOV (mm)	150x150 / 180x180	180x180 / 180x180	180x180 / 180x180	220x186 / 240x240	150x150 / 180x180	150x150 / 180x180
Matrix	224x178 / 256x224	256x202 / 256x256	308x307 / 352x320	124x87 / 384x384	208x166 / 256x224	208x208 / 256x256
N° of slices	12 / 14	13 / 14	75 / 64	18 / 22	11 / 14	50 / 64
Slice thickness (gap) mm	3 (0.3) / 3 (0.5)	3 (0.3) / 3 (0.5)	1 (-0.5) / 0.8	3 (0.3) / 3 (0.5)	3 (0.3) / 3 (0.5)	1.4 (-0.7) / 0.8
TE (ms)	10 / 20	90 / 85	3.5 / 2.2	77 / 93	15 / 20	4.6 / 3.4
TR (ms)	550 / 580	3000 / 4733	7.1 / 6.1	3713 / 6109	550 / 580	25 / 10.1
Number of excitations	3 / 2	3 / 4	2 / 3	4 / 3	3	1 / 1
Echo train length	3 / 18	17 / 22	n.a.	44 / 28	n.a.	n.a.
Acquisition time (m:s)	3:20 / 4:28	3:39 / 3:52	4:25 / 5:40	4:57 / 2:33	4:37 / 6:33	4:20 / 2:22

Ax: axial plane; Cor: coronal plane; T1w: T1 weighted; T2w: T2 weighted; TSE: Turbo Spin Echo; FSE: Fast Spin Echo; SPIR: Spectral Presaturation with Inversion Recovery; FAT SAT: Fat Saturation; B-FFE: Balanced gradient waveform Fast Field Echo; FIESTA: Fast Imaging Employing STeady-state Acquisition; DWI: Diffusion Weighted Imaging; PROPELLER: Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (GE's radial k-space filling pattern used to reduce the effect of patient voluntary and physiologic motion and reduce magnetic susceptibility artifacts); SE: Spin Echo; Gd: sequence acquired after i.v. administration of gadolinium based contrast medium; FFE: Fast Field Echo; SPGR: SPOiled Gradient echo; m: minutes; s: seconds.

Siemens, balanced fast field echo (FFE) by Philips, and true steady-state free precession (SSFP) by Toshiba. 3D CISS sequences are very useful in the assessment of cranial nerves anatomical variations, pathologies and vascular conflicts and compressions. To evaluate the intracisternal tract of the 7th and 8th cranial nerves (CNs), oblique sagittal reformatted CISS images perpendicular the internal auditory channel are highly suggested (Figure 3). Thick slab MPRs using a maximum intensity projection (MIP) algorithm obtained from 3D CISS sequences are commonly used to visualize internal ear structures such as labyrinthine structures, the endolymphatic sac and to evaluate the extent of a cochlear dysplasia in cases of

congenital or developmental hearing loss (Figure 4). Poschl like plane is commonly used in pediatric cases when a cranial nerve deficiency is suspected. If a cholesteatoma is suspected, non-echo planar (EP) diffusion weighted imaging (DWI) sequence has been demonstrated useful in differentiating typical findings of middle ear and/or mastoid infections from cholesteatomas larger than 2 mm [21]. Non-EP DWI is also useful in post-surgical evaluations. Conventional EP-DWI are more sensitive to susceptibility artifacts which typically affect this region with little to no practical applications. Additional dedicated sequences should be considered in case of intracranial or nasopharyngeal extensions of a disease.

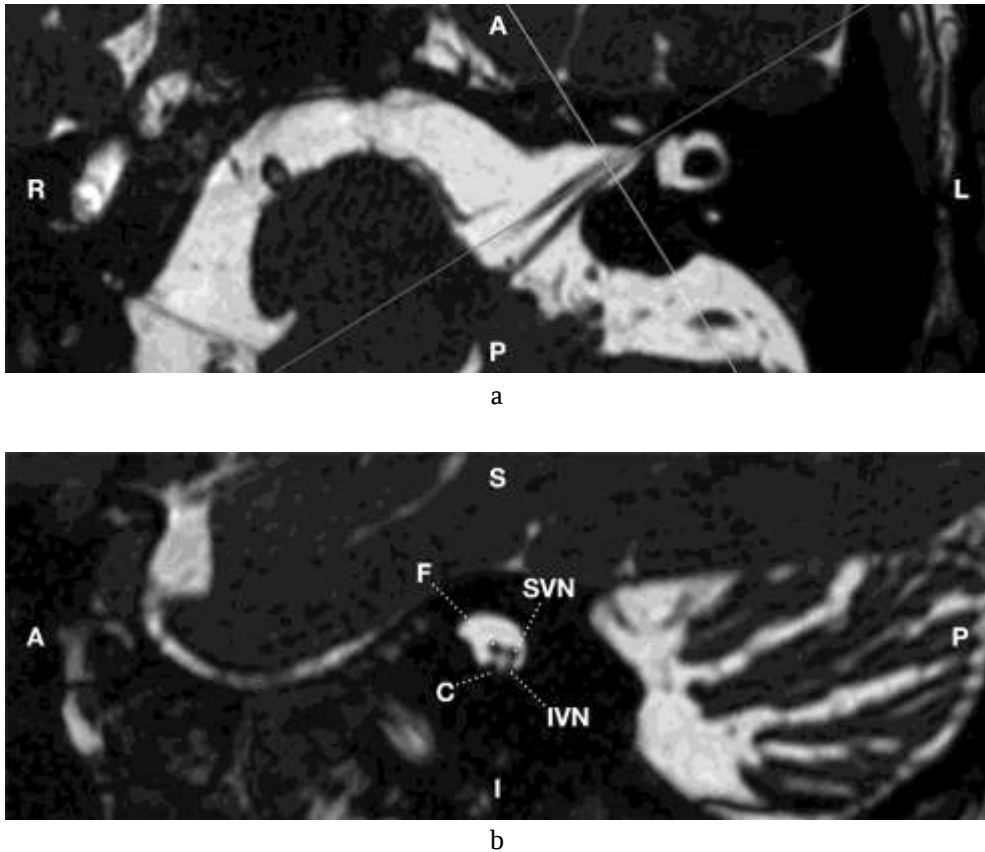


Figure 3. a) Axial 3D FIESTA passing through the left internal auditory channel (IAC) showing the intracisternal tract of the 7th (anterior) and 8th (posterior) cranial nerves; superimposed DICOM references lines shows the correct oblique orientation of a MultiPlanar Reconstruction (MPR) to evaluate the internal auditory channel tracts; b) the resulting MPR plane shows the typical four black dots into the IAC: the facial nerve (F) is in an anterior-superior location, the cochlear nerve (C) is in an anterior-inferior location, the superior and the inferior vestibular nerves (SVN and IVN respectively) are located posteriorly. A: anterior; P: posterior; S: superior; I: inferior.

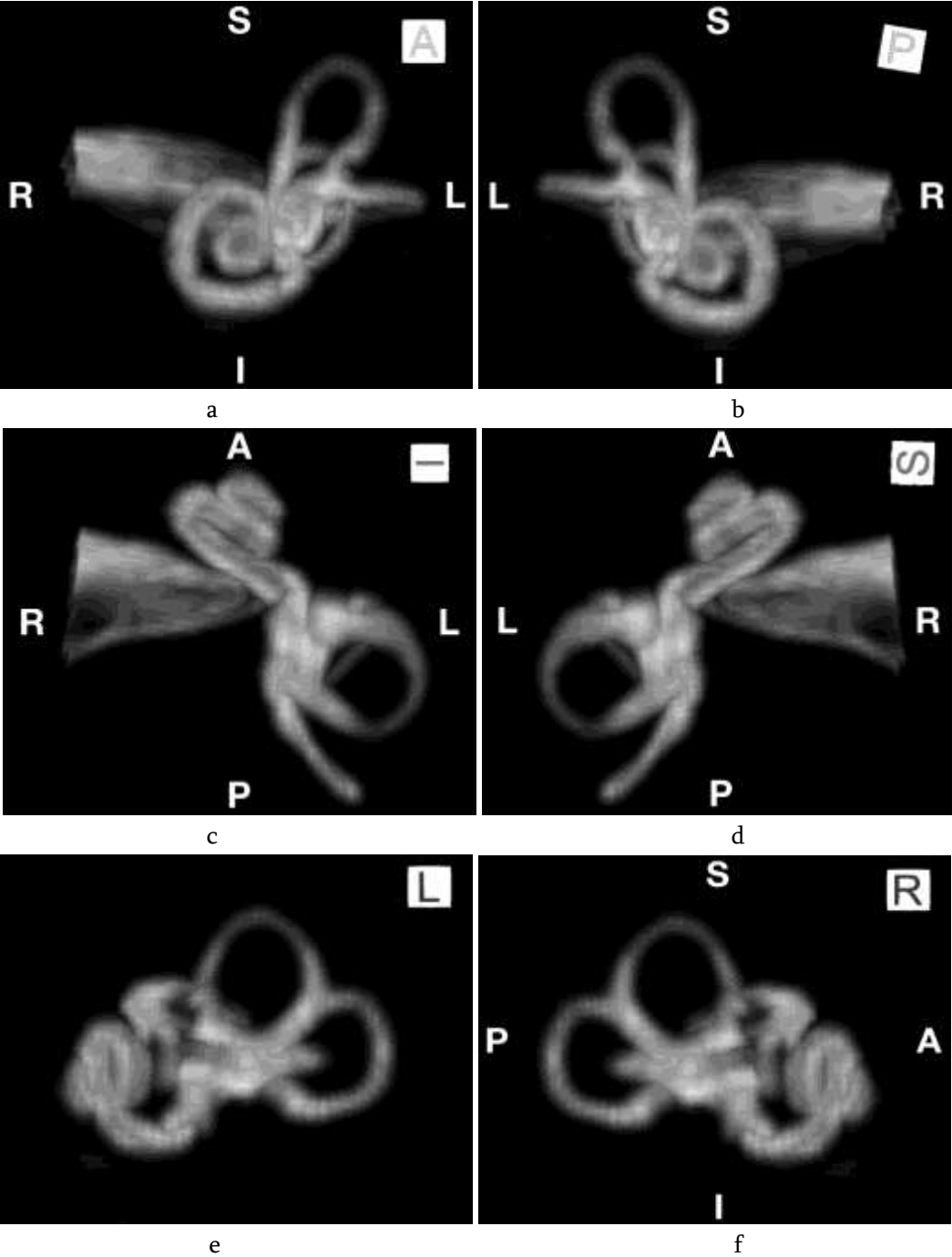


Figure 4. 3D Maximum Intensity Projection (MIP) reconstructions of the internal ear structures: anterior (a), posterior (b), inferior (c), superior (d), left (e) and right (f) orientations.

2. EXTERNAL EAR

Imaging plays a minor role in external ear pathology because it is usually evident at clinical evaluation. However, it becomes necessary if the EAC is obstructed or stenotic.

Aural dysplasia derives from a failure of the first branchial cleft to canalise EAC, implicating atresia or dysplasia. Clinical examination reveals a small and abnormal auricle (microtia) in association. In such cases, a CT scan is indicated before any surgical intervention to delineate the facial nerve canal. Aural dysplasia could be associated with congenital cholesteatoma or inner ear abnormalities which are usually minor [22, 23].

External otitis do not require imaging studies. If a necrotizing variant is present, imaging is recommended to evaluate periauricular involvement of the disease, because it spreads rapidly through bone and soft tissues. MRI is preferred if intracranial involvement is suspected [24].

In conductive deafness, stenotic EAC is sometimes difficult to evaluate, so a CT scan is required to exclude bone abnormalities such as fibrous dysplasia [25]. Fibrous dysplasia is a disease of young patients, conversely to esostosis that is usually in older people. Esostosis is a nodular elevation of bone involving tympanic bone, due to prolonged irritation of EAC secondary to cold water (Figure 5). Differential diagnosis includes osteoma that is usually seen as a unilateral, pedunculated bony lesion [26].

EAC cholesteatoma is rare; it is characterized by bony destruction and it usually has an iatrogenic origin after surgery. Trauma, focal osteitis, and cerumen retention are less frequent causes [27]. Keratosis obturans is an epidermal keratin plug in the EAC, often bilateral (Figure 6). On CT scan, it is a soft tissue mass associated with the widening of EAC, possibly with mild erosion of bony margins [28].



Figure 5. Bilateral EAC exostosis in a scuba diver with chronic exposure to cold water; coronal MPR of a MDCT scan show broad-based circumferential bony overgrowth of the osseous EAC (arrows) that severely reduces the width of the EAC (courtesy of Dr Giuseppe Tagliavia, “Centro di Radiologia Diagnostica srl” – Sciacca, Agrigento – Italy).

External ear cancers are rare; they demonstrate clinical symptoms similar to external otitis at the onset. They usually are squamous cell carcinoma or basocellular carcinoma. CT are required to evaluate surgical intervention; bone involvement is critical to surgical planning, especially when extending to temporomandibular joints or the middle ear. MRI is frequently associated in order to exclude perineural, perivascular or intracranial spread of the disease (Figure 7) [29, 30].

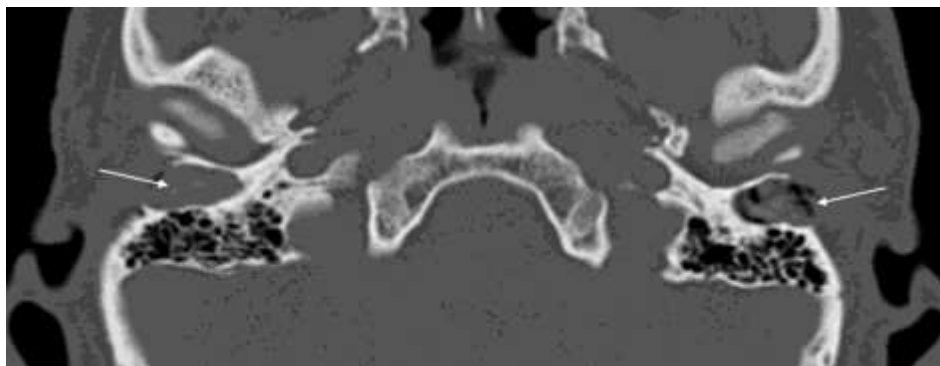


Figure 6. Bilateral EAC keratosis obturans; axial MDCT scan show bilateral soft tissue mass (arrows) within the bony EAC which enlarges the canal with no signs of bony erosion.

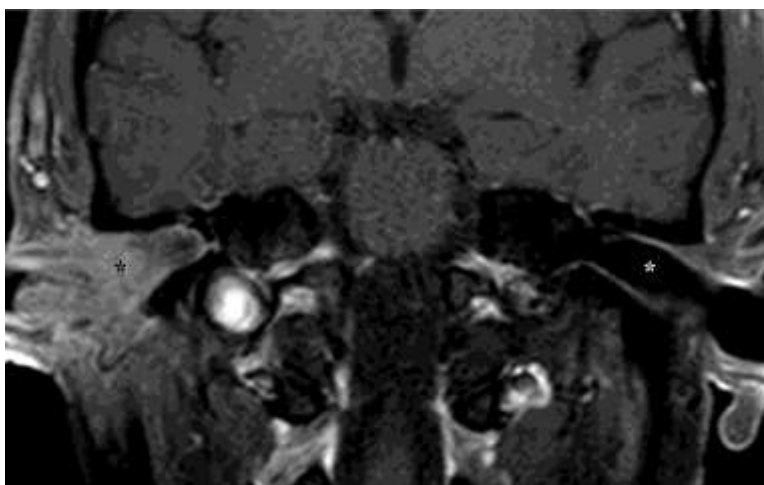


Figure 7. External ear cancer; coronal T1-weighted sequence with fat saturation acquired after i.v. administration of contrast medium. Contrast enhancing soft tissue mass (black asterisk) with undefined edges causing stenosis of right EAC and reaches the bony part of the EAC. Normal appearing contralateral EAC shows typical low signal due to its air content (white asterisk).

3. MIDDLE EAR AND MASTOID

The most frequent request for oto-neuroradiological examinations concern the middle ear.

The middle ear (or tympanic cavity), is the small, air-filled cavity, within the temporal bone located between the eardrum (tympanic membrane, TM) and the lateral bony wall of the internal ear. The tympanic cavity posteriorly communicates, through the *aditus ad antrum*, with the mastoid *antrum* and cells; anteriorly it communicates with the nasopharynx through the auditory tube (also known as Eustachian or pharyngotympanic tube) that allows it to equalize the air pressure inside the drum with atmospheric pressure lateral to the drum.

The tympanic cavity contains the three auditory *ossicles* (hammer or *malleus*, anvil or *incus* and stirrup or *stapes*) which transmit sound vibration from the tympanic membrane to

the inner ear enabling the primary function of the middle ear itself (sound-conducting apparatus). Other components of the tympanic cavity are tendons of the *tensor tympani* and the *stapedius* muscles, the *chorda tympani* (branch of the facial nerve) and tympanic plexus (branches from facial and glossopharyngeal nerves).

The tympanic cavity is bounded by six walls which must be carefully evaluated during the assessment of oto-neuroradiological examinations: superior (or *tegmen tympani* or *paries tegmentalis*), inferior (or jugular wall or *paries jugularis*), anterior (or carotid wall), posterior (or mastoid wall), lateral (or *paries membranaceus*) and medial (or *paries labyrinthica*). The tympanic cavity is also divided into three levels: *epitympanum* (level above the TM; it houses the body of the malleus and the incus), *mesotympanum* (TM level; is the central and the biggest compartment of the middle ear cavity, it houses the long processes of malleus and incus, the stapes, oval and round windows, facial nerve and parts of the middle ear muscles and tendons) and *hypotympanum* (level below the TM, it houses no functional elements) [31]. In adults the tympanic cavity measures approximately $15 \times 15 \times 6$ mm but the width in the center part of the cavity is only 2 mm [32].

High resolution CT/MDCT imaging of the temporal bone represent the first line imaging modality for middle ear evaluation, surgical treatment planning and post-therapy follow-ups. MRI is usually performed as a second level investigation for specific clinical suspects.

3.1. Congenital Anomalies of the Middle Ear

Middle ear anomalies can be unilateral or bilateral but they are predominantly unilateral (70-90%). The incidence of middle ear malformations is approximately 1 in 3800 newborns. The etiopathogenesis of most malformations of the middle ear is still poorly defined. In all genetically determined malformations (syndromal and non-syndromal) one can assume a high frequency of spontaneous genetic mutations. The acquired ear malformations originate from exogenic injury during pregnancy. The noxae could comprise infections, chemical agents, malnutrition, radiation exposure, Rh incompatibility, hypoxia, atmospheric pressure changes and noise exposure. Deficiency or malfunction of the thyroid hormone can be also associated with ear malformations. However, in many cases, the actual cause is unknown [33].

Middle ear malformations are a rare cause of conductive hearing loss in children, especially when these conditions are not associated with malformations of the external ear. These anomalies are usually confused with serous otitis [34]. The clinical and surgical relevance of these disorders are strictly related to the associated anatomical development anomalies and malfunctions [31].

If a congenital conductive hearing loss (CCHL) is suspected, a high-resolution CT examination in order to evaluate the bony structures of the middle ear should be considered.

Congenital anomalies of the middle ear can be classified into major (associated with an involvement of the tympanic membrane and external ear) and minor (exclusive involvement of the middle ear) [34].

Minor middle ear anomalies include a change in the anatomy or size of the tympanic cavity or a reduced distance between anatomical structures of the middle ear and fixated ossicles (stapes ankylosis). In major anomalies, the ossicles are often involved. The most common isolated ossicle deformity involves the *stapes* suprastructure in terms of aplasia or hypoplasia, thickening, thinning or fusion of the *stapes crura* [33]. The *malleus* tends to be

rarely involved in isolated middle ear malformations. The most frequent findings are deformities and hypoplasia of the head and of the manubrium of the malleus, fixations in the epitympanic recess and malleolo-incudal joint abnormality. The malleus can also be absent [31]. *Incus* malformations are dominated by absence or hypoplasia of the long process coexisting with incudo-stapedial joint separation. Less frequently, the long process may vary in position (horizontal rotation and fixation in the direction of the horizontally running tympanic segment of the facial nerve) or complete incus aplasia may be found. In addition, synostotic or synchondrotic incudo-malleolar joint abnormalities and epitympanic recess fixation have often been found [33].

The inner ear windows may be involved in middle ear anomalies in terms of a mobile stapes footplate or dysplasia/aplasia of the round or oval window. There may be anomalies of the oval window and, rarely, of the round window. Congenital agenesis of the oval window involves complete osseous obliteration of the oval window either by a concentric narrowing that produces a dimple-like depression along the medial tympanic wall or by a thick bony plate [33]. Almost 76% of the patients with congenital absence of the oval window presents with associated malformation of the facial nerve canal. The nerve can either limit the exposure of the oval window or it can cover the footplate completely. This condition may also be associated with conductive hearing loss [35].

Malformation and aberrant course of the facial nerve are frequently encountered; the common abnormalities include complete dehiscence of the tympanic segment, inferior displacement of the tympanic segment, and anterior and lateral displacement of the mastoid segment. The latter frequently obscures the round window.

Other malformations of the middle ear include a missing antrum, a pneumatized mastoid, cerebral spinal fluid (CSF) fistulas (indirect translabyrinthine or direct paralabyrinthine), congenital cholesteatoma (as known as congenital epidermoid), congenital dermoids, aberrant courses of arteries and veins, and malformations of the middle ear muscles.

The primary (congenital) cholesteatoma (Figure 8) counts as a congenital middle ear anomaly; a four-stage classification is used:

- *Stage I*: only one quadrant of tympanic membrane is affected with no ossicular involvement or mastoid extension;
- *Stage II*: multiple quadrants are affected but no ossicular involvement or mastoid extension;
- *Stage III*: ossicular involvement (includes erosion of ossicles and surgical removal for eradication of disease); no mastoid extension;
- *Stage IV*: mastoid extension (regardless of findings elsewhere).

Numerous classifications for middle ear malformations have been proposed. The classification of the minor malformations, proposed by Teunissen and Cremers [36], is based on the surgical aspects of the malformations, and subdivides them into four main groups:

- 1) Ankylosis or isolated congenital fixation of the stapes (footplate fixation and superstructure fixation);

- 2) Stapes ankylosis associated with other malformations of the ossicular chain (deformities of the incus and/or malleus, or aplasia of the long apophysis of the incus and bone fixation of malleus and/or incus);
- 3) Congenital anomalies of the ossicular chain with mobile stapes footplate (disruption of the ossicular chain, epytimpanic fixation or timpanic fixation);
- 4) Congenital aplasia or severe dysplasia of the oval and round windows (aplasia, dysplasia, prolapse of facial nerve or persistence of stapedia artery).

Kösling [37] described three degrees of severity of isolated middle ear malformations:

- 1) *Mild* malformations are those in which normal configuration of the tympanic cavity coexists with ossicular dysplasia;
- 2) *Moderate* malformations are characterized by hypoplasia of the tympanic cavity along with rudimentary or aplastic ossicles;
- 3) *Severe* malformations show aplastic or cleft-like tympanic cavity.

High-resolution CT is the best diagnostic imaging examination since it allows a correct visualization of bony structures. However, exploratory tympanotomy is the method that most reliably establishes the definitive diagnosis. All of these anomalies can be surgically corrected [31].

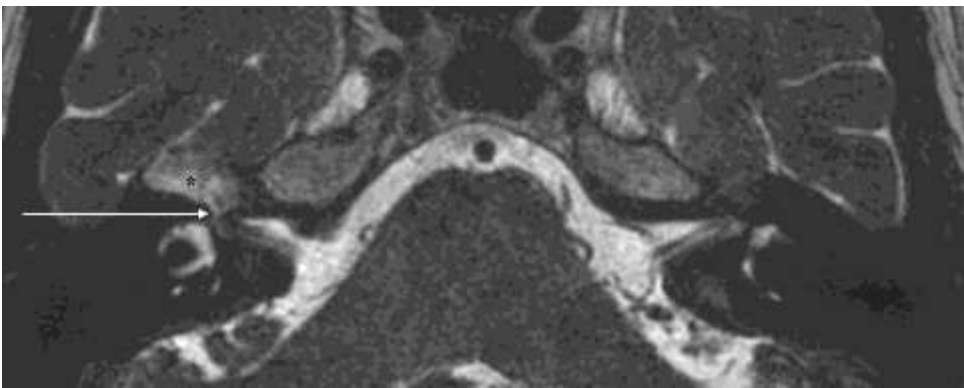


Figure 8. Primary (congenital) supralabyrinthine cholesteatoma; axial CISS sequence passing through the IACs showing the cholesteatoma (black asterisk) with a inhomogeneous low- to high- signal with geniculate ganglion impairment (white arrow).

3.2. Acute Infections of Middle Ear

Infection of the middle ear cavity is termed otitis media; it is called otomastoiditis (OM) when inflammation process spreads to the mastoid. Otitis media could occur suddenly (acute otitis media, AOM) or, if it does not go away or happens repeatedly, could remain over months to years (chronic otitis media, COM).

A mixture of factors predisposes to otitis media, but Eustachian tube dysfunction is thought to be one of the most important factors. Congenital palate defects, host immunity, and viral or bacterial infection may all be contributing factors.

AOM is commonly seen in children and it is the most common bacterial infection among children.

Although AOM is generally considered a bacterial infection, there is ample evidence that respiratory viruses have a crucial role in the etiology and pathogenesis of this disease.

The presence of viruses in the middle ear fluid is important not only in regard to the aetiology and pathogenesis of acute otitis media, but also in regard to the outcome of the disease [38].

Symptoms include earache, fever, pain, otorrhea, conductive hearing loss (CHL) with a bulging and red tympanic membrane at otoscopy [39].

Although this infection can be well estimated on otoscopic examination, further questions concerning the extent of the disease, exact location, structures involved and possible bone erosion, will be addressed in detail only with neuroradiological examinations. CT is the imaging modality of choice for the assessment of CHL [40].

In AOM, high resolution temporal bone CT is routinely performed and may reveal soft tissue in the middle ear cavity (Figure 9), thickened tympanic membrane with bulging. Other features that could be seen in AOM include air-fluid level in the middle ear (effusion) and bony erosion [39]. MR is indicated when complicated inflammatory lesions are suspected to extend into the inner ear or towards the sigmoid sinus or jugular vein. MR is very sensible in identifying typical high signals from fluid collections in the middle ear cavity and mastoid antrum on T2-weighted pulse sequences.

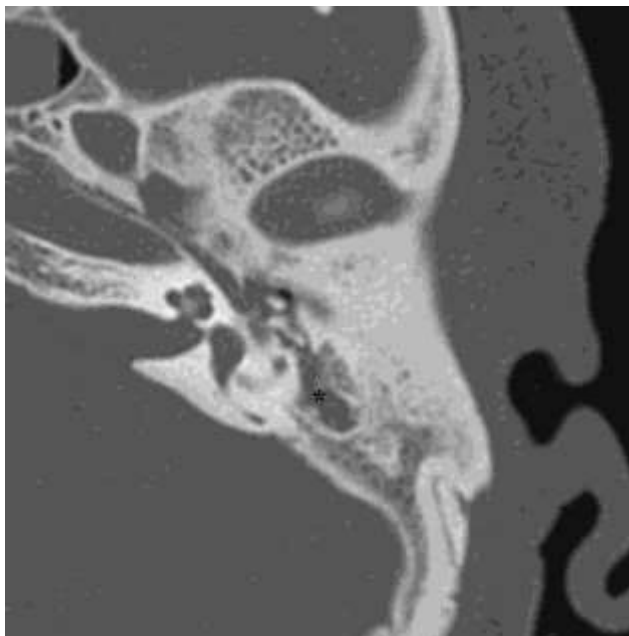


Figure 9. Acute otitis media; axial MDCT scan at the level of the IAC / middle ear showing soft tissue density in the middle ear cavity which extends to incorporate the ossicular chain and mastoid antrum (asterisk). Patient with a noticeable hypopneumatization of the temporal pyramid.

The clinical course of AOM is generally short: in the vast majority of patients the response of the immune system and the sensitivity of the germ to the administered antibiotic will be enough. However, acute otitis media can progress to severe complications, including acute mastoiditis, meningitis, and intracranial abscess [41]. In these cases contrast enhanced CT is useful to evaluate adjacent vascular structures such as the transverse sinus. MRI is mandatory if the intra-cranial dissemination of the inflammation process is suspected for a prompt diagnosis of cerebritis foci or to better characterize brain abscesses (late cerebritis).

Acute mastoiditis (AM), even if it could occur as an isolated process, is usually a complication of otitis media (Oto-Mastoiditis, OM) in which infection in the middle ear cleft involves the muco-periosteum and bony septa of the mastoid air cells. CT is usually the initial technique of choice for imaging patients with OM. Typical imaging findings are opacification of the tympanic cavity, mastoid antrum and air cells with bone erosion and/or destruction of the intramastoid bony septa (Figure 10) [42]. Contrast agent administration is recommended for better evaluation of perimastoid soft tissues and to exclude fearsome complications like dural venous sinus thrombosis [43]. MRI is mainly reserved for the detection, or detailed evaluation, of intracranial complications of OM. Typical MRI findings in patients with complicated OM are:

- opacification of the tympanic cavity and the mastoid with fluid-like signal intensity of intramastoid contents on T1- and T2-weighted imaging;
- diffusion weighted imaging (DWI) may show variable degrees of signal increase within the mastoid effusions; however, DWI is a mandatory sequence to detect purulent secretions and brain abscesses that are characterized by a bright signal intensity and a low signal on apparent diffusion coefficient (ADC) maps due to a restricted diffusion of water molecules movements within purulent collections;
- after administration of i.v. contrast, an intense intramastoid enhancement is commonly seen among the outer periosteum or the perimastoid dura.

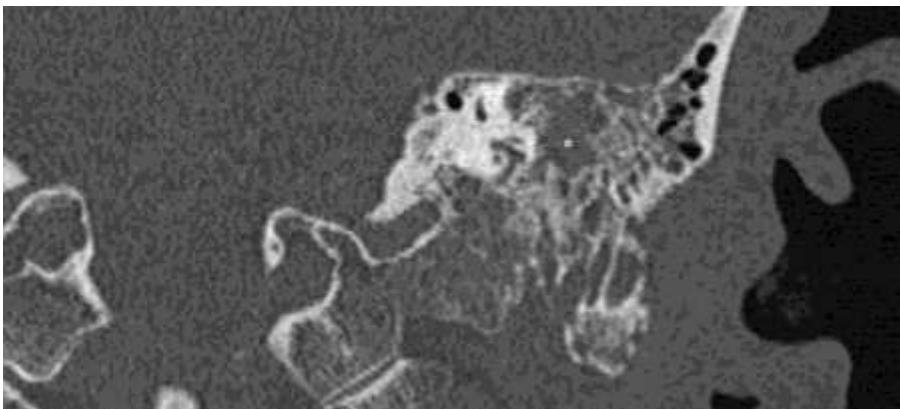


Figure 10. Patient with acute otomastoiditis; coronal MPR from a MDCT scan show typical soft tissue density into the middle ear cavity (asterisk) and mastoid cells with sign of erosion towards the infratemporal fossa (Bezold abscess).

According to Platzek [44], the diagnosis of AM is possible with a sensitivity of 100%, a specificity of 66% and an accuracy of 86%, with two of the following intra-mastoid findings on CT/MRI examinations: fluid accumulation, enhancement, or diffusion restriction.

In clinical practice, contrast-enhanced CT is still the preferable, first-line imaging technique due to higher accessibility, especially for urgent cases. Thus, MRI is:

- an alternative diagnostic tool for patients with contraindications to contrast-enhanced CT;
- a mandatory second level investigation to detect intracranial complications;
- recommended for paediatric patients due to its lack of ionizing radiation.

3.3. Chronic Otitis Media

The definition of chronic otitis media (COM) is based on clinical and pathological features.

When the inflammation of the middle ear persists at least 6 weeks and is associated with otorrhea through a perforated tympanic membrane, the diagnosis of chronic otitis media is placed.

Principal etiopathological factors of COM are infections of the upper respiratory tract, insufficiency of ciliary clearance and drainage of the Eustachian tube (Eustachian tube dysfunction), allergic history and familial predisposition. Symptoms include conductive hearing loss, vertigo, otorrhea and sometimes pain.

Chronic otitis media are classified in chronic suppurative otitis media (CSOM) and chronic otitis media with effusion (COME) [45].

CSOM is characterized by recurrent or persistent ear discharge (otorrhea) over 2 to 6 weeks through a perforation of the tympanic membrane.

COME is defined as the presence of fluid in the middle ear without symptoms or signs of infection and is the most common cause of acquired hearing loss in childhood.

Enabling an optimal visualization of bony structures and pneumatized spaces, CT is therefore the best diagnostic method to evaluate the involvement of temporal bone structures in patients with chronic inflammation of the middle ear [46].

On CT examination typical radiological signs of chronic otitis media are [39]:

- opacification or mucosal thickening in the tympanic cavity;
- obliteration of the epitympanum or Prussak's space by fibrous-inflammatory tissue (for tubal dysfunction, reduced transmucosal gas exchange, and development of otitis media);
- bone erosions and/or ossicular disorders;
- sclerosis and loss of aeration of the mastoid air cells;
- osteolysis of the bony septa and, in severe cases, osteomyelitis of the petrous temporal bone.

Since some ears with chronic inflammation develop cholesteatoma, chronic otitis media may be also classified into two groups: with or without cholesteatoma. Cholesteatoma is a well-demarcated non-neoplastic lesion resulting from an abnormal accumulation of squamous epithelium usually found in the middle ear cavity and mastoid process of the temporal bone [45].

3.3.1. Chronic Otitis Media without Cholesteatoma

Post-inflammatory ossicular chain fixation is a common finding in patients with chronic otitis media and conductive hearing loss (Figure 11). On CT images, three distinctive forms of ossicular chain fixation can be evaluated:

- presence of fibrous tissue, usually in the niche of oval window, forming a so-called “peristapedial tent” (fibrous tissue may also be present anywhere in mesotympanum and epitympanum).
- tympanosclerosis, which reflects deposits of hyalinised collagen in the tympanic cavity. If it occurs in the tympanic membrane, it is called myringosclerosis. In the tympanic cavity, it may be present in any location, visible as focal calcified densities in the middle ear cavity, along tendons, also in direct apposition to the ossicular chain.
- formation of new bone, rarely seen in the tympanic cavity, usually in epitympanum. Visible as high density lamellar structures.

Post-inflammatory ossicular chain erosion is rather rare in the case of a non cholesteatomatous disease but may seldom occur and will affect first the incus long process and lenticular process, followed by stapes head [47].

For best diagnostic accuracy on CT, images should be viewed using a correct bone window setting (large window width, e.g., 4000 HU; low window level, e.g., 0–200 HU).

Three distinctive signs should be carefully evaluated on axial CT images in order to exclude an ossicular erosion [39]:

- “ice cream cone” visible in the epitympanum, where the anterior ice cream cone consists of the malleus head and the posterior cone is made of the incus body and short process;
- “two parallel lines” visible in the mesotympanum, where the anterior line represents the malleus handle and the posterior line represents the incus long process;
- “two dots” visible in the mesotympanum where the lateral dot refers to the lenticular process and the medial dot to the stapes head; between the two dots the incudo-stapedial joint is well visible.



Figure 11. Chronic otomastoiditis with tympanosclerosis; axial MDCT scan showing non cholesteatomatous soft tissue density within the middle ear cavity and mastoid opacification. In this case calcific middle ear foci (arrow) is causing ossicular fixation resulting in conductive hearing loss; non cholesteatomatous ossicular chain erosion findings are present too.

Post-inflammatory erosion sometimes involves walls of tympanic cavity. Based on CT multiplanar images, the following structures should always be carefully evaluated: bony walls of the lateral semicircular canal, bony walls of the tympanic segment of the facial nerve channel and the roof of the middle ear cavity (*tegmen tympani*) [39].

3.3.2. Chronic Otitis Media with Cholesteatoma

Occasionally, chronic suppurative otitis media is associated with a cholesteatoma within the middle ear. Cholesteatoma consists of squamous epithelium that is trapped within the middle ear cavity and mastoid process of the temporal bone. Granulation tissue and ear discharge are often associated with secondary infection of the desquamating epithelium [48]. In the setting of chronic middle ear inflammation, cholesteatomas arise as the result of tympanic membrane retraction or perforation [39].

Cholesteatoma can be either congenital (behind an intact tympanic membrane) or acquired, though the origins are indistinguishable with histology or imaging. Only the location of the lesion on CT/MRI, the clinical history of the patient, and the otologic status of the tympanic membrane could give some hints for a differential diagnosis [21]. If untreated, a cholesteatoma may progressively enlarge and erode the surrounding structures [45].

Since congenital cholesteatomas develop from embryonic epithelial rests, they can be located everywhere in the temporal bone from the external auditory channel to the middle ear, from the mastoid to the petrous apex or even in the squama of the temporal bone or within the tympanic membrane.

Acquired cholesteatomas are classified in primary and secondary but are uniquely localized in the middle ear (see Table 3):

- **“Primary acquired cholesteatomas”** (80% of all middle ear cholesteatomas) usually develop in the region of the pars flaccida behind an apparently intact tympanic membrane;
- **“Secondary acquired cholesteatomas”** (18% of all middle ear cholesteatomas) usually develop into the middle ear through a perforated tympanic membrane in the

pars tensa region (rarely the pars flaccida); these cholesteatomas arising from the posterior tympanic membrane are likely to produce facial nerve exposure eroding the bony wall of the facial nerve canal and to destroy the stapedial suprastructure.

Table 3. Pars flaccida and pars tensa cholesteatomas main features

Pars flaccida cholesteatoma (attic or posterior epitympanic cholesteatoma)	Pars tensa cholesteatomas (sinus or posterior mesotympanic cholesteatoma)
Develop from the upper one-third portion of the tympanic membrane (pars flaccida or Shrapnell membrane).	Most often origins through a defect of the lower two-thirds portion of the tympanic membrane (pars tensa)
Soft tissue mass fills the Prussak's space, medial to attic wall and lateral to the ossicles (head of malleus and body of incus).	Soft tissue mass localized in the facial recess and sinus tympani of the tympanic cavity and in the mastoid region.
Erosion of the anterior portion of the lateral epitympanic wall is very common.	Extension of the soft tissue mass starts in the epitympanum medial to the ossicles
Initially ossicles are very often displaced medially.	Initially ossicles are displaced laterally (head of malleus and body of incus).
Ossicles erosion is frequent (most commonly long process of incus).	Ossicle erosion occurs to incus long process, stapedial superstructure and manubrium of malleus.

In elderly patients, a third special kind of cholesteatomas could be diagnosed: external auditory channel cholesteatomas. These lesions are subdivided into idiopathic and secondary [50]. The first are typically bilateral and located in the floor of the external auditory channel. The location and occurrence of the latter depends on the site of the inducing factor.

One last special group of cholesteatomas are the so called “mural cholesteatoma.” These could mimic a mastoidectomy cave since they are the result of extensive lesions of the middle ear or of the mastoid which drain their fluid contents into the external auditory channel through the tympanic cavity leaving a wide empty cave often referred to as “automastoidectomy” [21].

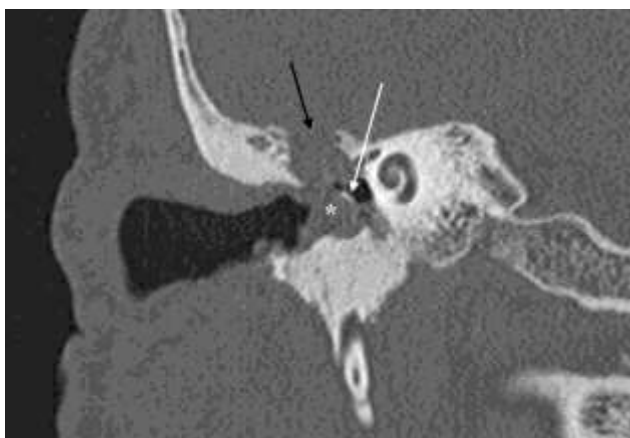


Figure 12. Chronic otomastoiditis with cholesteatoma; coronal MPR from a MDCT scan showing soft tissue density within the middle ear cavity (asterisk) with severe thinning of the tegmen tympani (black arrow), ossicular chain dislocation and severe erosion (white arrow).

When evaluating CT images for the presence of cholesteatoma (Figure 12), the following features should be addressed: ossicle erosion and displacement, bony walls of tegmen tympani and lateral semicircular canal, bony walls of tympanic segment and anterior genu of the facial nerve, possible extension of cholesteatoma towards sinus tympani and possible involvement of oval window niche [21].

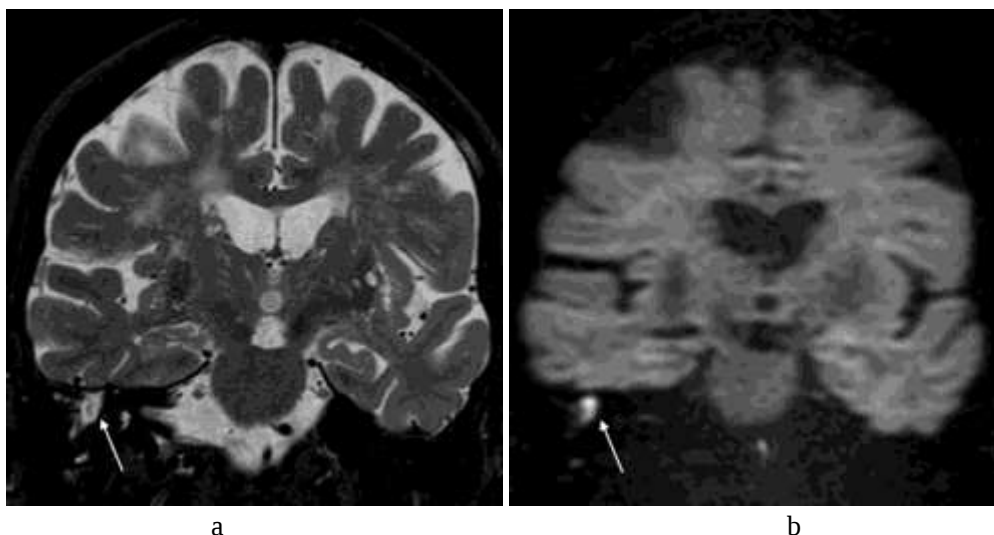


Figure 13. Chronic otomastoiditis with cholesteatoma (same patient shown in figure 12); coronal T2-weighted fast spin echo sequence with fast saturation (a) showing unspecific high signal intensity inflammatory tissue in the middle ear cavity (white arrow). A coronal non-echo planar DWI sequence (b) well demonstrate the cholesteatoma within the unspecific fluid collection as a bright comma shaped lesion (white arrow).

On MR images (Figure 13), typical cholesteatoma features include bright, hyper-intense signal on diffusion-weighted MRI images (low signal on apparent diffusion coefficient maps), moderate signal intensity on T2-weighted images (lower than the signal that characterize the inflammatory tissue) and lack of enhancement on post-gadolinium T1-weighted sequences [21,49-50].

Chronic otitis media can cause both intracranial and extracranial complications [51,52].

The most frequent complications of COM with cholesteatoma are [21]:

- erosion of the tegmen or sinus plate that could be thinned or completely eroded;
- erosion of the labyrinth with fistula formation appreciable as a loss of the endochondral bone overlying the labyrinth (labyrinthine fistula occurrence is one of the most common complications in chronic otitis media with cholesteatoma);
- extension of the cholesteatoma into the petrous pyramid;
- erosion of the facial nerve canal commonly resulting in a peripheral facial nerve paralysis.

Sigmoid sinus thrombosis is a severe complication of chronic middle ear infectious diseases. In these cases, a contrast enhanced CT scan is mandatory to demonstrate the typical “empty triangle” or “delta” sign: the sigmoid sinus will appear surrounded by the normally enhancing dura that delimitate the un-enhancing thrombus inside the dural venous sinus [53]. MRI is more sensitive to detect thrombosis and assess intraluminal blood flow, and it may even show the involvement of adjacent structures.

In case of suspected infection/inflammation and/or complications (such as lateral semicircular canal fistula), an MRI examination including non-echo planar diffusion-weighted (non-EP DWI) and post-gadolinium T1-weighted sequences is mandatory. These will help differentiating the infection/inflammation from the cholesteatoma and it will show the status of the membranous labyrinth.

Since chronic otitis media with cholesteatoma (including precholesteatomatous states) is an aggressive form of otitis, surgical treatment is mandatory because of the higher risk for labyrinthine or intracranial complications.

The differential diagnosis checklist in case of suspected cholesteatomas includes: cholesterol granulomas, paragangliomas, schwannomas and facial nerve hemangioma (see Table 4).

Table 4. Most common pathologic entities to consider for cholesteatomas differential diagnosis

Pathologic entities	Cholesterol granulomas	Paragangliomas	Schwannomas (facial nerve and geniculate ganglion)	Facial nerve hemangiomas
MRI findings	- High signal on T1-w and T2w. - No contrast-enhancement.	Nodular contrast-enhancing mass on the cochlear promontory.	Characteristic tubular/oval enhancing mass along the tympanic segment of the facial nerve or of the geniculate ganglion.	-Mass with irregular poorly defined margins -Slightly hypointense/isointense on T1WI and hyperintense on T2WI -Bright contrast-enhancing oval lesions on postcontrast images.
CT findings	Bony erosion.	No bony erosion.	Enlarged facial nerve canal and/or geniculate fossa.	-Enlarged facial nerve canal and geniculate fossa. -The ossifying subtype causes a characteristic “honeycomb” morphology.
Others	-Blue tympanic membrane at otoscopic examination. - History of surgery or recurrent otitis media. - Usually DWI does not show diffusion restriction.	- Pulsatile mass at otoscopic examination. Common clinical symptom is rhythmic thumping in the ear.	Large tumors involving the tympanic segment of the facial nerve may be visible on otoscopic examination.	Primary symptoms are facial nerve palsy and hearing loss.

3.4. Post-Operative Imaging

Surgery is widely used to treat various middle ear disorders such as chronic otitis media, cholesteatoma, otosclerosis, congenital malformations, traumas and tumours. The most common cause of failure in middle ear surgery include persistent suppurative process in middle ear / mastoid and recurrent and/or residual cholesteatoma [54]. Imaging needs to be able to differentiate residual or recurrent disease from granulation tissue, inflammatory tissue or fluid within the middle ear cavity and mastoid cavity. The examination of choice for a post-surgical follow-up is usually a non-contrast high-resolution temporal bone CT which provides information on the exact surgical procedure done and related findings [55-56]. The main role of CT is to allow a correct analysis of dense structures (bony tympano-mastoid walls, ossicular chain, prosthesis) [42]. Furthermore, CT easily detects an intra-tympanic soft tissue and its extension and margins within the postoperative middle ear. However, CT is not specific and so differentiation of granulation tissue in the middle ear cavity from other commonly encountered soft tissue masses such as cholesteatomas usually requires an MRI scan [56]. Despite this, CT is of great help for the assessment of the bony labyrinth and the facial nerve canal.

Conventional MRI scans have low specificity when it comes to differentiating granulation tissue from relapsing cholesteatoma [57]. As a matter of fact both the granulation tissue and the cholesteatoma show hypointense signal on T1 and hyperintense signal on T2 making the differentiation rather difficult. Many studies reported improved specificity of delayed (30-45 minutes) post-contrast T1-weighted sequences since the granulation tissue is poorly vascularized and contrast uptake may occur belatedly [55]. Cholesteatomas are not vascularized and so do not enhance: they typically appear bordered by a ring enhancement attached to the enhancing mucosa [55]. Diffusion-weighted imaging (DWI) is a helpful and effective method for distinguishing cholesteatomas from other soft tissues in post-surgical follow-ups; in particular, non-echo planar DWI has been shown to have a higher sensitivity and specificity in the diagnosis of postoperative chronic otitis media complications differentiating recurrent cholesteatoma from granulation tissue [55, 58].

However, De Foer [41] reported that MR imaging for detection of middle ear cholesteatoma can be performed by using non-EP DW imaging sequences alone since the combined use of DWI and delayed gadolinium-enhanced T1-weighted sequence yielded no significant increases in terms of sensitivity, specificity, negative and positive predictive values.

Some non-cholesteatoma lesions that show restricted diffusion have been reported in English literature and must be taken into account in the differential diagnosis checklist: residual haemorrhage after recent surgery, in ear patches containing silastic sheets or bone pate, cerumen located in the external ear canal, cholesterol granuloma and middle ear or mastoid abscess [55].

Pre-contrast T1-weighted sequences are mandatory to detect lesions with spontaneous high T1 signal intensity (cholesterol granuloma, fluid with high protein concentration, bleeding and fatty tissue) and to get information about the vascularity of the lesion. Fat suppression techniques may result useful too if the lesion is close to a fat containing structure. A careful analysis of the T1-weighted pre- and delayed post-contrast, T2-weighted images and DWI provide a sensitive and accurate method for differentiating soft tissue lesions. The

most informative approach to imaging of post-surgical middle ear patients is the use of both CT and MR imaging examinations [55].

3.5. Otosclerosis

Otosclerosis is an autosomal dominant genetic disease with incomplete clinical penetrance and variable expression which involves the human otic capsule [59]. The typical clinical onset is in the third decade and is characterized with symptoms of conductive hearing loss (CHL) due to the impaired movement of the stapes; the disease is bilateral in a majority of cases with a female predilection (F:M ratio of ~2:1) [60]. Patients could also present sensorineural hearing loss (SNHL) or mixed hearing loss (MHL) and/or tinnitus [61]. Pathogenesis of otosclerosis is likely multifactorial and still incompletely understood: even if the genetic component is probably the most significant in determining the slowly progressive CHL, both viral (measles virus) and autoimmune (collagen auto-immunity) etiopathogenetic hypothesis have been investigated and accredited. Whatever the etiopathogenesis, otosclerosis is one of the leading causes of nonsyndromic deafness in adults [62-64].

Otosclerosis is an otodystrophy characterized by the replacement of the normal ivory-like enchondral bone of the otic capsule by immature and spongy vascular new bone; this process of remodeling occurs continuously and accounts for the progressive nature of the disease [65].

It is categorised into two types, fenestral and retrofenestral (or cochlear) otosclerosis. Retrofenestral otosclerosis rarely occurs without fenestral involvement and is considered a continuum of the fenestral otosclerotic process rather than a separate one. Imaging plays an important role in the diagnosis and management of otosclerosis.

In fenestral otosclerosis, demineralized foci of spongy bone typically occur in the region located anterior to the oval window (*fissula ante fenestram*) where a cleft of fibrocartilagenous tissue between the inner and middle ear is found (Figure 14). These typical demineralised foci location should not be confused with the so called “cochlear cleft” [66] that is particularly seen in up to 40% of children as a hypodense cleft in the cochlear otic capsule in the region anterior to the oval window; this finding has no pathological implication in the absence of a clinical evidence for otosclerosis or osteogenesis imperfecta and represent a potential imaging pitfall in children.

In patients with fenestral otosclerosis, fixation of the stapes by foci located anterior to the oval window is found in 96% of cases. In slightly less than half the cases, demineralised foci are also present in other locations (oval window niche 30%, cochlear apex 12%, posterior to the oval window 12%); in 7% of cases a round window obliteration is found. Other even rarer sites of involvement are the promontory, round window niche and tympanic segment of the facial nerve [61]. CT is the tool of choice to investigate the eventual presence of otosclerotic lesions and its sensitivity to make the diagnosis was recently estimated as high as 90–95% [66]. Stapedectomy is used to treat fenestral otosclerosis and is commonly combined with the insertion of a stapes prosthesis to restore ossicular chain functionality. CT is useful to evaluate the position of radiodense prosthesis (dislocation is a common possible complication) and the typical findings of other post-surgical common complications. MRI will be useful to identify fibrotic changes in cases of labyrinthitis ossificans (Figure 15) [61].



Figure 14. Fenestral otosclerosis; axial MPR from a MDCT scan showing an otospongiosis focus (arrow) close to the round window (not shown).

Retrofenestral (or cochlear) otosclerosis, is much less common but nearly always associated with fenestral otosclerosis. Primary cochlear otosclerosis is relatively rare. The typical clinical presentation is a bilateral symmetrical SNHL or MHL or a pulsatile tinnitus. Demineralized foci of spongy bone are typically seen in the cochlear capsule, which may extend around the vestibule, semicircular canals and internal auditory canal (Figure 16). The classical imaging appearance of cochlear otosclerosis on CT is a distinctive pericochlear hypodense double ring sign (which is also known as the “4th ring of Valvassori”) [61].

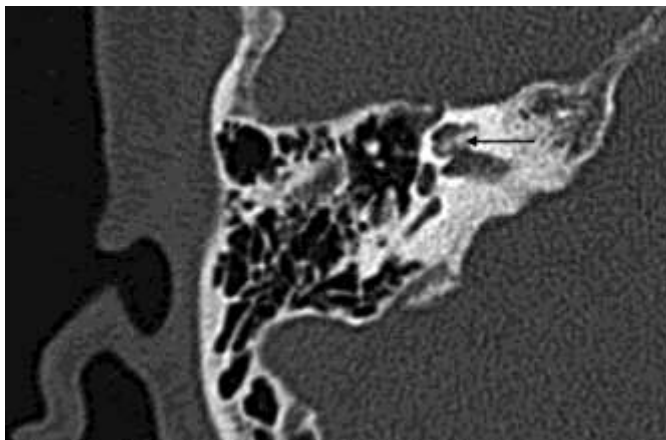


Figure 15. Labyrinthitis ossificans (arrow) could involve any part of the inner ear, in different grade (mild, moderate as shown in the figure, and severe). It is a sequela of an inflammatory process spreading into the membranous labyrinth through three ways: hematogenic, meningogenic (as shown in the figure), and tympanogenic disseminations. Unusual cause of labyrinth ossification are temporal trauma, long standing otosclerosis or tumors. It is a relative contraindication for cochlear implant.



Figure 16. Cochlear otosclerosis; coronal MPR from CBCT scan showing the demineralized foci (arrows) around the basal turn of the cochlea in the otic capsule.

MRI is rarely used in the case of otosclerosis but is useful to demonstrate the osteolytic inflammatory process (during the “acute phase” of the disease) that occurs in the otic capsule as a consequence of the otospongiotic process. During this phase, the otospongiotic foci will show a T1 shortening on MRI pulse sequences acquired after i.v. injection of gadolinium. MRI is also useful to investigate post-surgery complications (intravestibular granuloma, intralabyrinthine hemorrhage and bacterial labyrinthitis) [68].

Fluorides and cochlear implantation (CI) are used to treat retrofenestral otosclerosis. Fluoride therapy may limit the growth of active otosclerotic foci and thereby prevent progression of SNHL. CI surgery in patients with otosclerosis may be challenging because of the high risk of partial insertion and misplacement of electrode arrays due to the ossification of the scala tympani in the basal turn of the cochlea [61].

4. INNER EAR

The inner ear is composed of a membranous labyrinth surrounded by a bony labyrinth.

The membranous labyrinth consists of utricle, saccule, semicircular canals, endolymphatic sac and duct, and cochlear duct [69]. CT and MRI may well demonstrate the inner ear structures and their abnormalities. CT has always been the preferred imaging modality to delineate the intricate osseous anatomy and malformations of the inner ear, but high-resolution MR imaging is used with increasing frequency to study the membranous labyrinth and eighth cranial nerve (vestibulocochlear nerve) [70–71].

4.1. Malformations

Congenital abnormalities of the inner ear are the most common cause of sensorineural hearing loss (SNHL). Inner ear malformations (IEMs) occur as a result of an interruption of the development of the ear itself during the first trimester of fetal development. The causes may be idiopathic, associated with an inborn genetic error or due to a teratogenic agent exposure [72]. The findings may be isolated or related to a specific syndrome (Table 5). Patients with congenital inner ear malformations often present with a variable degree of

SNHL. Roughly 50% of cases of congenital SNHL can be linked to a genetic cause, with approximately 30% of these considered syndromic and the remaining 70% being nonsyndromic [73]. The abnormalities are usually bilateral and symmetric; these patients are commonly affected by a profound SNHL that could benefit from the use of hearing aids or may have an indication for a cochlear implant (CI).

Table 5. Hereditary syndromes commonly associated with SNHL and characteristic imaging findings

Hereditary syndrome associated with SNHL	Related imaging findings
Alagille syndrome	absence of the PSCC with normal appearing LSCC
Branchio-oto-renal syndrome	Cochlear hypoplasia (apical turn); abnormal course of the facial nerve canal; funnel-shaped IAC with large porus acousticus; vestibular dysplasia; SCC hypoplasia; enlargement of the vestibular aqueduct; cochlear nerve deficiency; stenosis or atresia of the external auditory canal; middle ear and ossicular chain abnormalities; Eustachian tube dilation; absence of the stapedius muscle.
CHARGE syndrome	Small misshaped pinnae; small middle ear cavities; absence of the stapedius muscle; absence of the round and oval windows; hypoplasia of the incus and stapes; ossicular chain fixation; abnormal course of the tympanic facial nerve; SCC aplasia with associated vestibular dysplasia; cochlear nerve deficiency with atresia of the cochlear aperture; abnormalities of cochlear partitioning.
Klippel-Feil syndrome	Small pinnae with stenotic and downward sloping EEC; deformed caput mallei; rudimental incus head; shortness or absence of long process and absence of the whole incus; missing stapes head; fixed footplate; absence of footplate or of the the whole stapes.
Pendred syndrome	Modiolar deficiency; vestibular enlargement; absence of the interscalar septum between the upper and middle cochlear turn; endolymphatic sac enlargement.
Waardenburg syndrome	Vestibular aqueduct enlargement; widening of the upper vestibule; IAC hypoplasia; decreased modiolus size; aplasia or hypoplasia of the PSCC.
X-linked hearing loss with stapes gusher	Enlarged bulbous IACs; widened cochlear aperture (appearing as wide as communication between the basal turn of the cochlea and the IAC) with absence of the lamina cribrosa; cochlear hypoplasia with modiolar deficiency; widening of the bony canal for the labyrinthine segment of the facial nerve; dilation of the vestibular aqueducts.

Congenital malformations of the inner ear may be considered in two broad categories [74]: (a) malformations with pathologic changes that involve only the membranous labyrinth and (b) malformations that involve both the osseous and the membranous labyrinth (malformed otic capsules).

The majority of the causes of congenital hearing loss (80%) belong to the first group. There is no gross bony abnormality and, therefore, in these cases HRCT and MR imaging of the temporal bone reveal normal findings. The remaining 20% have various malformations involving the bony labyrinth and can be radiologically demonstrated by CT and MRI. In patients who are candidates for CI surgery, imaging provides preoperative information about the inner ear, the vestibulocochlear nerve, and the brain. CT and MRI together, can aid decision making about the best management strategy by facilitating the identification and characterization of inner ear malformations and any associated neurologic abnormalities.

Formerly, the Jackler et al. classification of IEMs was based on the time of developmental arrest during embryogenesis and anatomical development [75]. In 2002 Sennaroglu et al. [76] modified this classification and grouped the inner ear anomalies by their decreasing severity; Michel deformity (complete labyrinth aplasia), cochlear aplasia, common cavity, incomplete partition type 1 (IP-I or cystic cochleovestibular malformation), cochlear hypoplasia and incomplete partition type 2 (IP-II or classic Mondini deformity). There are a variety of IEMs and they all present in a different way: each group has different radiological findings that are very important in the management of deaf patients.

4.1.1. Complete Labyrinthine Aplasia (Michel deformity)

Complete Labyrinthine Aplasia (CLA) is a rare malformation resulting in complete aplasia of the membranous labyrinth. It is caused by the developmental arrest of otic placode, early during the third week of fetal development [77]. It is the most severe among the deformities involving the osseous and membranous labyrinth.

According to radiological findings [78], three subgroups of CLA are present:

- 1) *CLA with hypoplastic or aplastic petrous bone* - In these cases CLA is accompanied by hypoplasia or aplasia of the petrous bone.
- 2) *CLA without otic capsule* - In this group of CLA, formation of the petrous bone is normal, but the otic capsule is hypoplastic or aplastic.
- 3) *CLA with otic capsule* - Formation of the petrous bone and the otic capsule is normal. Only in this group of CLA with otic capsule development, the labyrinthine segment of the facial canal is in its normal location.

On CT examinations there is a complete absence of inner ear structures (cochlea, vestibule and semicircular canals). The external auditory canal and middle ear cavity are usually normal because they do not arise from the otic capsule. Vestibulocochlear nerve is aplastic in patients with Michel deformity because they have no otic vesicle development. Patients present with a complete SNHL [77].

4.1.2. Cochlear Aplasia

Cochlear aplasia is the absence of the cochlea with formation of the utricle, saccule and semicircular canals. CT demonstrates an absent cochlea with a partially or completely formed vestibule and semicircular canals (SCCs) (Figure 17).

There are two subgroups [79]:

- 1) *Cochlear aplasia with normal labyrinth* - Vestibule and SCCs are normally developed;
- 2) *Cochlear aplasia with a dilated vestibule (CADV)* - Vestibule and SCCs show dilatation.

It is very important to differentiate CADV from a common cavity (CC) deformity.

Cochlear aplasia with a normal labyrinth is usually symmetric. In CADV, however, asymmetric development may be present; pathology may be due to genetic or environmental factors. Otic capsule development is always normal.

4.1.3. Common Cavity Deformity

A common cavity results from a developmental arrest in the 4th week of gestation and accounts for about 25% of all cochlear malformations [71]. CC deformity denotes a malformed inner ear in which the vestibule and cochlea are confluent with no internal architecture. Theoretically, this structure has cochlear and vestibular neural structures. There may be accompanying SCCs or their rudimentary parts.

It is important to differentiate CC from CAVD because CI in a CC may result in acoustic stimulation, whereas in CAVD no functional stimulation will occur with CI.

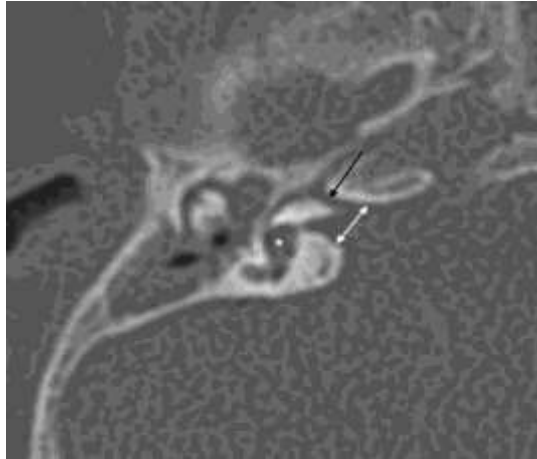


Figure 17. Cochlear aplasia associated with aberrant course of facial nerve; axial MDCT scan at the level of the IAC (double headed arrow). The cochlea is absent, a dilated vestibule can be identified (asterisk) and the intralabyrinthine segment of CN VII is antero-medially displaced (black arrow).

4.1.4. Cochlear Hypoplasia (CH)

In this deformity, there is a clear differentiation between cochlea and vestibule. In CH the dimensions are less than those of a normal cochlea with various internal architecture deformities. But the definition “cochlea with one and a half turns” should be used for hypoplasia (particularly type III), rather than for IP-II cochlea.

Patients have variable SNHL depending on the degree of development of the membranous labyrinth. CT shows a small cochlear bud, while the vestibule is usually enlarged. The SSCs are malformed in 50% of patients. Four different types of CH have been defined [80]: (i) *CH-I (Bud-like cochlea)*, (ii) *CH-II (Cystic hypoplastic cochlea)*, (iii) *CH-III (Cochlea with less than 2 turns)*, (iiii) *CH-IV (Cochlea with hypoplastic middle and apical turns)* (Figure 20).

4.1.5. Incomplete Partitions

In incomplete partition (IP) anomalies there is a clear differentiation between cochlea and vestibule, with normal external dimensions and various internal architecture defects. Incomplete partitions constitute 41% of IEMs [79, 80] There are three different types of incomplete partition groups according to the defect in the modiolus and the interscalar septa:

- 1) **IP-I** (termed as “cystic cochleovestibular malformation” [79]). These represent approximately 20% of IEMs. In this anomaly, there is a clear differentiation between cochlea and vestibule. The fact that the vestibule is distinguishable from the cochlea makes it possible to differentiate an IP-I from a common cavity. Cochlea is accompanied by an enlarged, dilated vestibule (Figure 18). The cribriform area between the cochlea and IAC is often defective, and all patients have a large IAC, predisposing them to increased risks for meningitis. All patients with IP-I and recurrent meningitis who have normal tympanic membranes but fluid filling the middle ear and mastoid, should have an exploration of the middle ear with special attention to the stapes footplate.
- 2) **IP-II** (classic Mondini deformity). In IP-II, the apical part of the modiolus is defective (Figure 19). It is the most common type of cochlear malformation, accounting for more than 50% of all cochlear deformities [74]. This anomaly was originally described by Carlo Mondini, and together with a minimally dilated vestibule and an enlarged vestibular aqueduct (EVA) constitute the triad of the Mondini deformity. The term “Mondini” should be used only if the above mentioned triad of malformations is present [76,81]. The apical part of the modiolus and the corresponding interscalar septa are defective, giving the apex of the cochlea a cystic appearance due to the confluence of middle and apical turns. The external dimensions of the cochlea are similar to that seen in normal cases. Therefore, it is not correct to define this anomaly as a cochlea with “one and a half turns” [80].
- 3) **IP-III**. In IP-III, cochlea has an interscalar septa but the modiolus is completely absent. IP-III cochlear malformation is the type of anomaly present in X-linked deafness [82]. It is the rarest form of incomplete partition cases, among 2% of all IEMs. The external dimensions of the cochlea (height and diameter) were found to be similar to the normal cochlea [83].

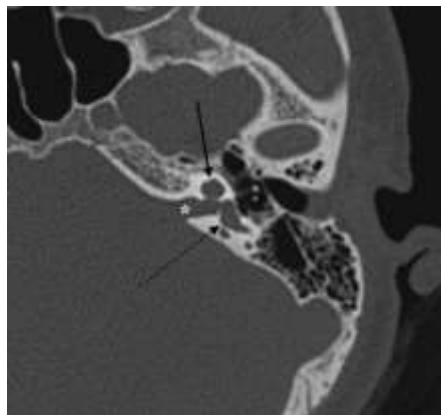


Figure 18. Incomplete partition type I (IP-1); axial MDCT scan showing typical cystic appearance of the cochlea and vestibule (severe case). The cochlea (black arrow) is featureless because of the absence of the modiolus and the interscalar septum; coexists vestibular dilatation (dotted arrow) and a wide IAC (asterisk).



Figure 19. Incomplete partition type II (IP-II); axial MDCT scan. The apical part of the modiolus is defective giving the typical cystic appearance of the apex of the cochlea because of coalescent apical and middle turn (arrow). The defective modiolus is appreciable only in proximity of the medial side of the basal turn (dotted arrow). Coexists vestibule (asterisk) and vestibular aqueduct (white arrow) dilatation.

4.1.6. Enlarged Vestibular Aqueduct (EVA)

This describes the presence of an enlarged vestibular aqueduct in the presence of a normal cochlea, vestibule and SCCs (Figure 20). The difference between EVA and IP-II is that cochlea and vestibule are completely normal on HRCT and MRI [80]. Classically EVA is described when the midpoint between posterior labyrinth and operculum is larger than 1.5 mm on axial sections.

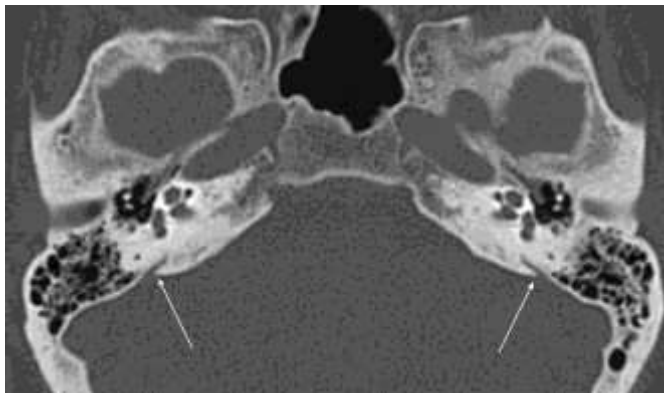


Figure 20. Patient with congenital sensorineural hearing loss with an enlarged vestibular aqueduct syndrome; axial MDCT scan showing bilateral slight enlargement of vestibular aqueduct and its operculum (arrows).

4.1.7. Malformations of the Vestibule and Semicircular Canals

The malformed canals are usually short and wide but may be narrow. In extensive malformations, the vestibule is dilated and forms a common lumen with the lateral canal. This type of abnormality, which has been described as “lateral semicircular canal–vestibule

dysplasia,” may be accompanied by a normal or malformed cochlea, depending on the stage of inner ear development at the time of embryologic arrest.

Aplasia of the semicircular canals is far less common than dysplasia. Absence of all semicircular ducts occurs frequently in patients with CHARGE syndrome (a combination of coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies) [84, 85]. Isolated aplasia of the posterior semicircular duct has been described in patients with Waardenburg syndrome and Alagille syndrome [84].

It is essential to perform high-resolution CT to confirm the diagnosis of semicircular canal aplasia and to differentiate it from fibrous or calcified obliteration of the canals.

4.1.8. Abnormalities of the Vestibulo-Cochlear Nerve

With current MRI technique, it is possible to visualize the vestibulo-cochlear nerve. It may be normal to hypoplastic or absent (Figure 21). The absence of the cochlear nerve is definitely found in cochlear aplasia. While in the case of Michel deformity with absent IAC, the complete vestibulo-cochlear nerve is also absent and only facial nerve can be identified.

An hypoplastic vestibulo-cochlear nerve is particularly important in CC.

The amount of cochlear nerve fibers determines the hearing level and management strategy.

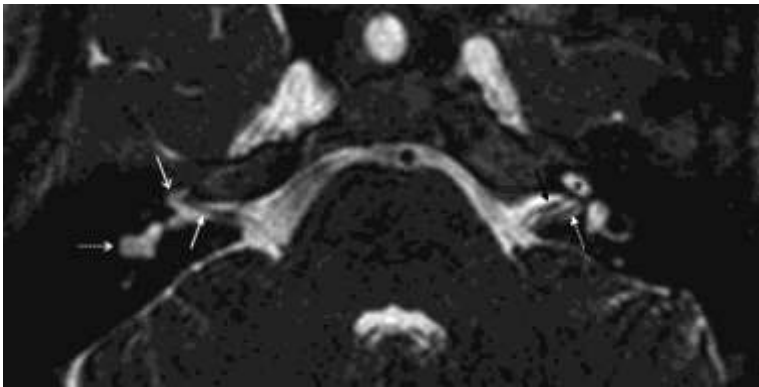


Figure 21. Cochlear nerve aplasia; axial 3D CISS sequence at the level of IACs showing right cochlear nerve aplasia with ipsilateral small bud cochlea (white arrow with empty head) and vestibular and lateral semicircular canal malformation (dotted line with empty head); the right facial nerve (white arrow) is antero-medially displaced. The left vestibulocochlear nerve (black arrow and white dotted arrow) is unremarkable as well as the visualised sections of the cochlea (basal turn, asterisk).

4.2. Infections

The inner ear infections usually refer to an inflammatory process of the membranous labyrinth, which typically manifests as an acute SNHL or vertigo. Labyrinthitis can be classified on the basis of the causative agent and can be considered infectious (bacterial, viral, or luetic) or non-infectious (trauma, autoimmune, or toxic).

A number of viruses, including measles, mumps, influenza, rubella, cytomegalovirus, and herpes are associated with acquired inner ear pathology [86]. CT and MRI are complementary in evaluating patients with labyrinthitis.

On the ot-neuroradiological point of view, three stages are described in labyrinthitis:

- 1) *Acute stage*: MR imaging demonstrates strong labyrinthine enhancement on gadolinium-enhanced T1-weighted imaging; however, enhancement is not specific for an infectious aetiology because similar findings can be seen with non-infectious causes of labyrinthitis. On CT, the inner ear appears normal.
- 2) *Fibrous stage*: on CISS sequences is seen as loss of the normal fluid signal intensity in the membranous labyrinth [87]. Contrast-enhanced T1WI may demonstrate enhancement of the inner ear, not as strong as that in the acute phase. On CT, the inner ear will appear normal.
- 3) *Ossifying stage*: it appears on CT as calcification within the inner ear. MR imaging will demonstrate loss of normal hyperintense fluid signal intensity on CISS images, without enhancement on contrast-enhanced T1WI [88].

Fibrosing and ossifying labyrinthitis may be indistinguishable on MR imaging, and CT is necessary to determine the presence of inner ear ossification. This distinction is particularly important in candidates for cochlear implantation (CI) because significant ossification of the cochlea can make implantation more difficult, if not impossible, and often results in poor functional results [89].

When ossification of the labyrinth becomes very advanced, there may be no recognizable labyrinthine structures, in which case the chief differential consideration is labyrinthine aplasia.

4.3. Autoimmune Labyrinthitis

The diagnosis of autoimmune labyrinthitis is usually one of exclusion. Patients typically present with rapidly progressive fluctuating bilateral SNHL that responds to immunosuppressive agents. Usually these patients also have autoimmune disease such as Cogan syndrome, systemic lupus erythematosus, juvenile idiopathic arthritis, Wegener granulomatosis, Sjogren syndrome or antiphospholipid syndrome.

Autoimmune labyrinthitis appears similar to infectious forms of labyrinthitis on MR imaging and will demonstrate intense labyrinthine enhancement acutely on postcontrast T1WI [87, 88]. The imaging abnormalities often resolve with steroid treatment but may occasionally progress to fibrosing or ossifying labyrinthitis.

4.4. Imaging in Cochlear Implantation

Cochlear implantation (CI) is indicated for some patients with profound SNHL. Preoperative knowledge of the anatomic features of temporal bone may be critical for making the decision to perform CI. The majority of cases of SNHL result from degeneration of the hair cells in the organ of Corti. CI devices bypass the hair cells and directly stimulate the spiral ganglion cells. The electrode is inserted into the scala tympani via the round window or through an anteroinferior cochleostomy (Figure 22-23). Both MRI and high resolution CT in

combination can provide surgically relevant information [90]. The goal of preoperative imaging is primarily to identify cochlear abnormalities, eighth-nerve deficiency, or anatomic variations that influence candidacy, ear selection, surgical approach, and prognosis. Special attention should be placed on the patency of the round window, size of the facial recess, course of the facial nerve, patency of the cochlea and presence of IAC [91].

Cochlear anatomy, as well as the degree of residual hearing, may influence a surgeon's choice of electrode.



Figure 22. Cochlear implant visualization on plain film radiograph (Stenvers' view) performed for postoperative evaluation of a cochlear implant lead.

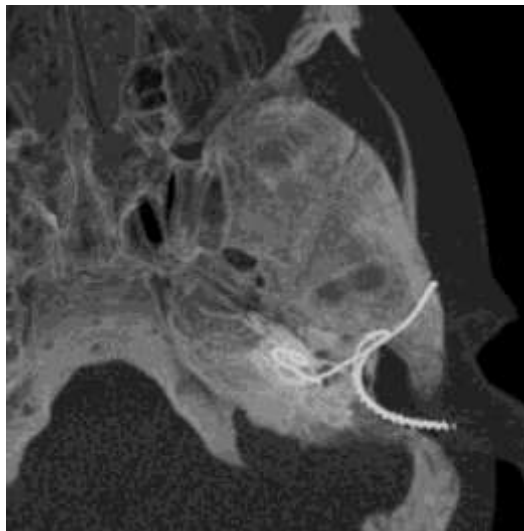


Figure 23. Cochlear implant in a patient with IP-II malformation; the image shows an axial thick-slab maximum intensity projection (MIP) reconstruction from a MDCT scan.

Once, evidence of an absent or severely dysplastic cochlear nerve, as in Michel deformity, was considered an absolute contraindication to cochlear implantation in any

patient. More recently, implantation in children with an absent or deficient eighth nerve was performed with variable results. A potential alternative treatment for children with cochlear nerve deficiency is auditory brainstem implantation [92].

Other conditions that may preclude CI are active otosclerosis and bilateral acoustic schwannomas. Of course, active middle ear infections and fluid in the middle ear cavity should be noted to delay surgery.

5. IMAGING OF CEREBELLOPONTINE ANGLE AND INTERNAL AUDITORY CANAL LESIONS

Lesions of the cerebellopontine angle (CPA) and internal auditory canal (IAC) are frequent and represent 6%–10% of all intracranial tumors. Vestibular schwannomas and meningiomas are the two most frequent lesions and account for approximately 85%–90% of all CPA tumors [93, 94]. The other 10%–15% represents a group of lesions arising from the different structures found in these anatomical regions.

The detection of lesions at CPA and IAC is a diagnostic challenge for neuroradiologists. The diagnostic study with the greatest sensitivity and specificity in the evaluation of asymmetric sensorineural hearing loss (aSNHL) is MRI.

Currently, the MRI screening protocol for CPA lesions consists of high-resolution T2-weighted (T2w) sequences (see Paragraph 1.2 for CISS sequences) in combination with contrast-enhanced T1-weighted (GdT1w) sequences.

T2w has a very high diagnostic accuracy for the presence of CPA lesions in patients with aSNHL. However, GdT1w remains mandatory in the detection of smallest vestibular schwannomas as well as rare differential diagnoses [95].

Common lesions of the IAC/CPA include vestibular schwannomas, meningiomas, haemangiomas, lipomas, lymphomas, facial nerve tumours, and aneurysms.

5.1. Vestibular Schwannoma

Vestibular schwannoma (VS) is the most frequent tumour in the CPA (70–80% of all CPA masses). It arises from the Schwann cells that wrap the vestibulocochlear nerve at the glial-Schwann cell junction (Obersteiner-Redlich zone). VS are usually unilateral, not hereditary and occur sporadically; bilateral vestibular schwannomas are usually associated with a genetic disorder (neurofibromatosis type 2, NF2).

Most vestibular schwannomas develop from the inferior vestibular nerve in the IAC where they grow slowly (Figure 24). Then, eroding the posterior edge of the porus acusticus, it may give rise to a round component in the CPA cistern, giving the typical “ice cream on cone” pattern (Figure 25). Small, purely intracanalicular schwannomas exist, but may also present with a dumbbell extension in the cochlea or vestibule [96]. On the other hand, purely intracisternal vestibular schwannomas, without IAC involvement, have a large space to grow in before becoming symptomatic, and at imaging are always larger and heterogeneous due to cystic components or bleeding [97].

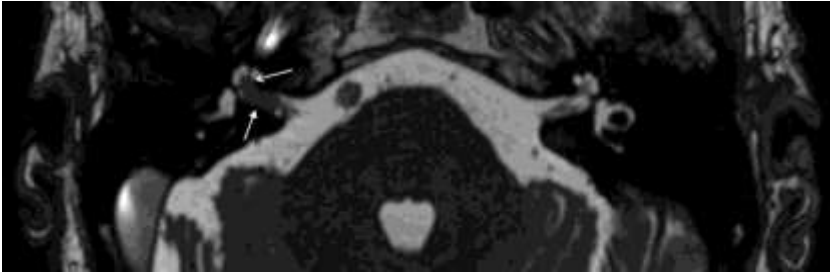


Figure 24. Intra-canal vestibular schwannoma; axial CISS at the level of IACs showing a small mass which arise from the modiolus region (empty head arrow) and extends up to two-third of the IAC (arrow).

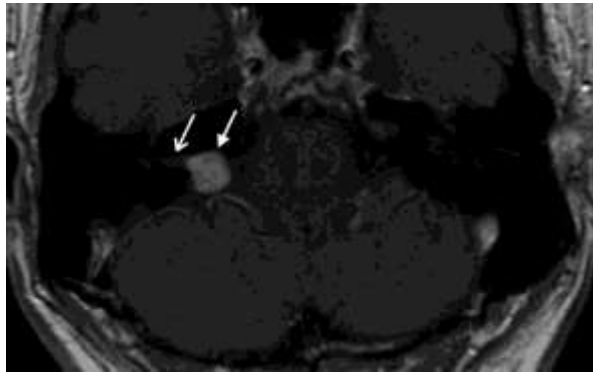
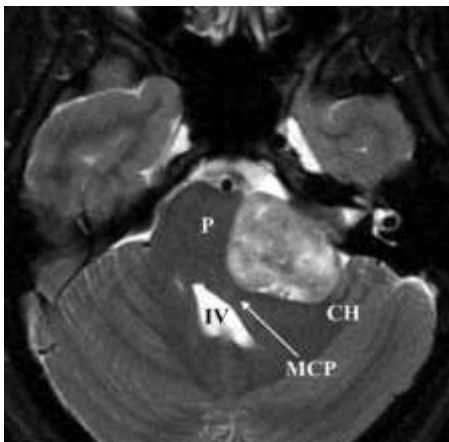
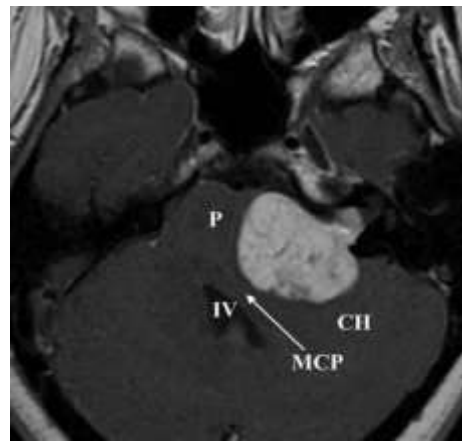


Figure 25. Vestibular schwannoma with typical “ice cream on cone” pattern; axial contrast enhanced T1-weighted sequence at the level of IACs showing an enhancing solid mass (arrow, the “ice cream”) which arise from the IAC (empty head arrow, the “cone”) and extends into the CPA cistern mass.



a



b

Figure 26. Giant solid vestibular schwannoma; axial T2-weighted turbo spin echo (a) and axial contrast enhanced T1-weighted spin echo (b) sequences at the level of left IACs showing a big solid mass extending from the IAC to the CPA cistern causing severe mass effect of the pons (P) and on the ipsilateral middle cerebellar peduncle (MCP) and cerebellar hemisphere (CH); the fourth ventricle (IV) is evidently compressed too.

With CT, schwannomas are usually isodense and enhance after contrast administration. On MRI, they show T1 isointensity and T2 high signal intensity (Figure 26), but appear as a hypointense filling defect on T2-weighted high-resolution MR cisternography (CISS sequences), and enhance strongly on Gd-T1w. Enhancement of the adjacent meninges is possible in vestibular schwannoma and is not specific nor exclusive for meningiomas [98].

There are three different MRI appearances of the tumor after Gd-administration: homogeneous (50–60%), heterogeneous (30–40%), and cystic (5–15%) [99].

MRI may also be used to optimize treatment planning with respect to several features of the lesion: (i) the size of the tumor; (ii) the distance between the lateral extremity of the intracanalicular portion of the tumor and the fundus because it affects the hearing prognosis and may modify the surgical approach; (iii) the intralabyrinthine signal intensity: poor hearing prognosis may be predicted by a low T2-signal intensity of labyrinth contents compared to the unaffected ear; (iv) the identification of the facial nerve and its position relative to the vestibular schwannoma [16].

5.2. Meningioma

Meningioma represents the second most frequent (10%–15%) tumor of the CPA after VS [94]. Meningioma arises from arachnoid meningotheelial cells and grows slowly in the CPA, independently from the internal auditory canal. It is usually located at the posterior aspect of the temporal bone or at the premeatal area, from where it can easily extend into the IAC, but without enlarging the porus [16]. At CT, meningiomas are hyperdense in 70% of the cases, calcified in about 20% and show a frequent adjacent bone reaction including hyperostosis and enostotic spur.



Figure 27. Skull base meningioma with multi-compartmental extension; axial T2-weighted turbo spin echo sequence with fat saturation. Heterogeneous mass with multiple intra-tumoral degenerative cysts and peritumoral arachnoid cysts (black asterisks). The tumour invades the pituitary fossa (white arrow) causing internal carotids arteries encasement (dotted arrows), the anterior cranial temporal fossa floor (white arrow with empty head) and orbital region, and the pontine and PCA cisterns extending into the right IAC (white asterisk) with basilar artery encasement (black dotted arrow) and mass effect on the pons and infratentorial brain structures with severe compression of the IV ventricle.

Meningiomas are isointense with the cortex on all sequences (Figure 27), and are strongly enhanced after i.v. contrast medium injection, usually homogeneously. The “dural tail sign,” is particularly frequent in association with meningiomas, but not specific [98] and should suggest the diagnosis when observed.

5.3. Aneurysms

The vertebral and basilar arteries and some of their branches pass through the CPA cistern, where a tortuous segment or ectasia or even an aneurysm can develop. They account for a substantial part of non-tumoral lesions of the CPA that can lead to cranial nerves or brain stem compression [93]. In this location, intracranial aneurysms can arise from the postero-inferior cerebellar artery (PICA), the antero-inferior cerebellar artery (AICA), the vertebral artery (VA) or the basilar artery (BA) itself [100].

They may mimic vestibular schwannomas, especially on CT, because they appear as well defined round lesions that enhance after contrast administration. At MRI, aneurysms without internal thrombus have flow voids and pulsation artefacts on all spin echo sequences but demonstrate iso-to-high signal intensities and variable patterns of gadolinium uptake on T1-weighted images when intraluminal thrombus is present. MR angiography should then be performed to confirm the diagnosis, detect the parent artery and plan the possible therapeutic options.

5.4. Epidermoid Cyst

The epidermoid cyst is the third most frequent tumor of the CPA [93]. It is a congenital lesion arising from normal epithelial cells included during neural tube closure. It grows from the slow desquamation of the stratified keratinised epithelium that lines the cyst.

These tumors grow slowly, encasing nerves and arteries in the cisterns with a specific cauliflower-like outer surface [17]. On CT scans, epidermoid cysts appear hypoattenuating to CSF, and have characteristic irregular, lobulated margins. As opposed to an arachnoid cyst, epidermoid cysts produce no reaction to the adjacent bone structures.

With MRI, epidermoid cysts have slightly higher signal intensity than CSF on T1w and T2w images. However, based on signal intensity alone, it could be difficult to distinguish from arachnoid cysts on these sequences. T2-weighted FLuid Attenuated Inversion Recovery (FLAIR) and Diffusion Weighted Imaging (DWI) sequences are well known to allow differentiation between epidermoid and arachnoid cysts (Figure 28). DWI offers a finding specific for epidermoid cysts by showing a very bright signal [101]. DWI is also crucial in the postoperative follow-up as it allows confirmation of the presence of a possible residual tumour.

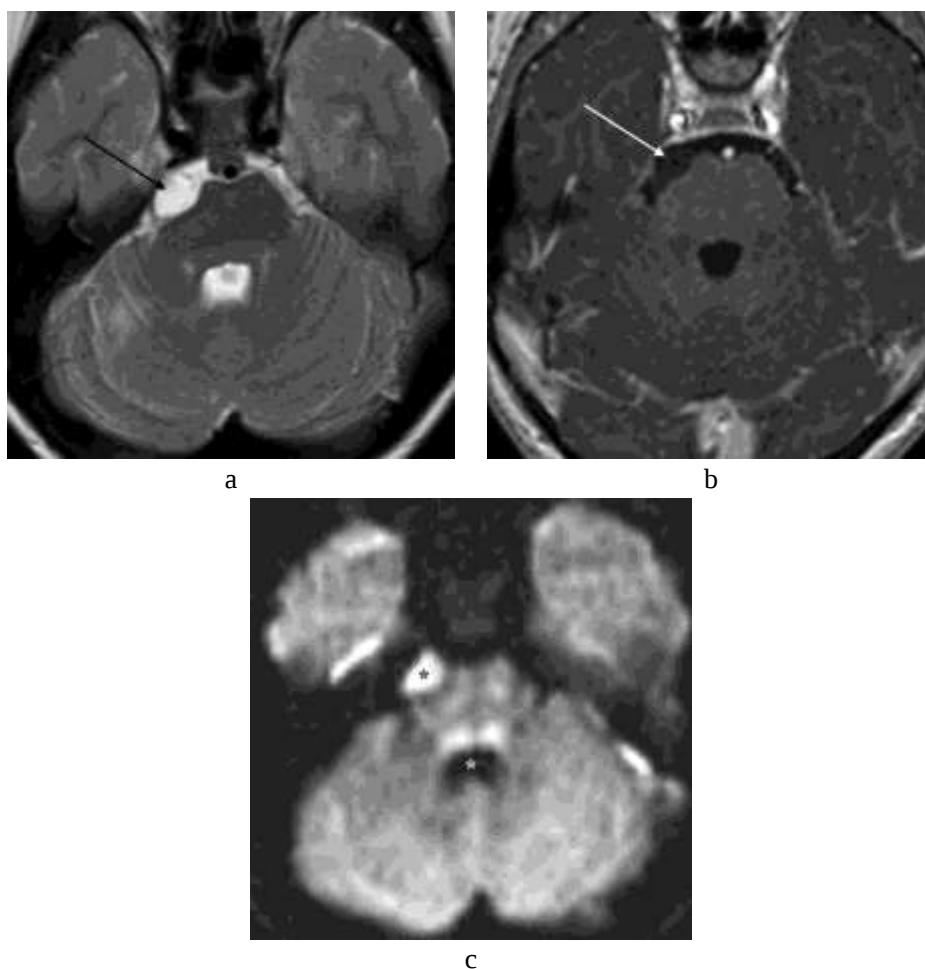


Figure 28. Epidermoid cyst; axial T2-weighted (a), contrast-enhanced T1-weighted (b) and echo planar DWI (c) sequences at the level of the CPA / pontine cistern. A small lesion with CSF like signal on T2 and T1+Gd in the right CPA / pontine cistern is shown (arrows). DWI highlights the finding which show a typical bright signal (black asterisk) if compared to CSF (white asterisk within the IV ventricle).

5.5. Arachnoid Cyst

An arachnoid cyst is a congenital, benign, intra-arachnoid pouch-like lesion filled with normal CSF. It is usually supratentorial, with about 70% being in the temporal fossa, mostly on the left side [17], anterior to the temporal poles. Only 10% of arachnoid cysts are located in the posterior fossa, where they most commonly develop in the CPA.

Spontaneous or traumatic intracystic haemorrhage can complicate arachnoid cysts, though this is uncommon in the posterior fossa [102].

At neuroimaging, attenuation and signal intensities of uncomplicated arachnoid cysts exactly match those of CSF on all sequences (Figure 29), and do not enhance after contrast media administration. The typical complete suppression of signal intensity on FLAIR sequence and the lack of diffusion restriction of these lesions on DWI easily help in the differential diagnosis with epidermoid cysts.

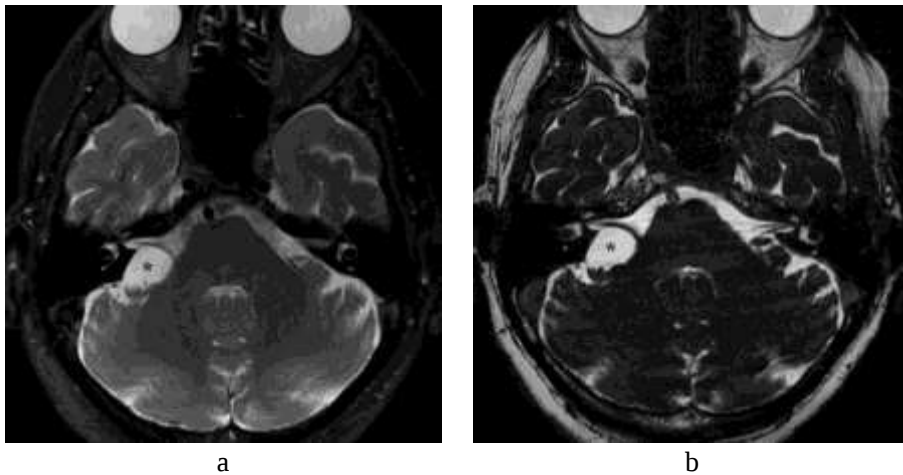


Figure 29. Arachnoid cyst; axial T2-weighted with fat-saturation (a) and high resolution CISS (b) sequences at the level of IACs. A lesion occupying the right CPA with CSF like signal on all pulse sequences is shown (asterisk); the cyst causes mild mass effect on the intracisternal tract of the vestibulocochlear nerve.

5.6. Lipochoristomas (Lipomatous Tumors)

Lipochoristomas are benign rare tumors (0.1% of all CPA tumours) that were thought to arise from cells of the meninx primitive and thus they were referred to as lipomas of the IAC/CPA. Nowadays they are more appropriately characterized as “lipomatous choristomas” since they arise from mesenchyme endogenous to the vestibulocochlear nerve [103]. They typically appear as homogeneous fatty lesions surrounding and encasing normal adjacent neurovascular structures with very dense adhesions, usually asymptomatic. Sometimes they may produce symptoms by compressing the adjacent cerebral structures, such as the cranial

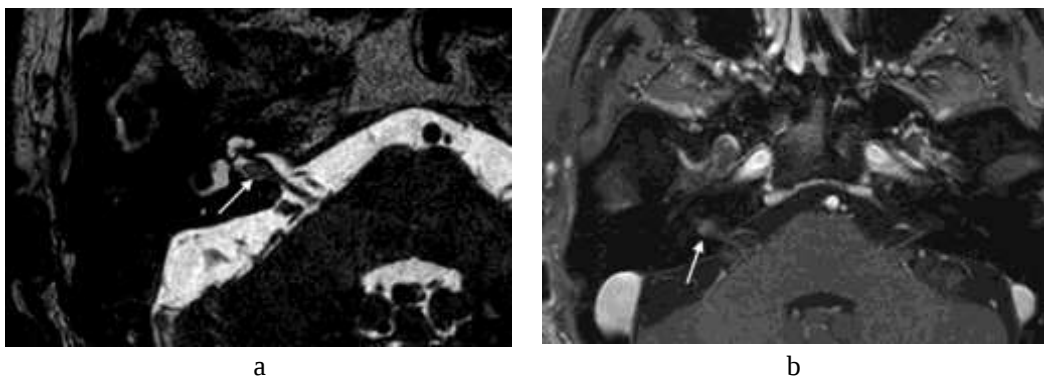


Figure 30. Lipochoristoma; axial CISS (a) and axial contrast-enhanced T1-weighted turbo spin echo sequence with fat saturation (b). A small lesion with fat-like signal on all pulse sequences is found (arrows) deep into the right IAC.

nerves [104]. Lipochoristomas typically show as hypoattenuating lesions on CT with a high signal on MRI T1-weighted images (promptly suppressed with fat saturations sequences) and no contrast enhancement on T1-weighted images acquired after i.v. administration of contrast medium (Figure 30). They usually show an indolent slow growth and conservative management with periodic imaging follow-ups is thus recommended. Those lesions which have a low fat content usually show an iso- or mildly hypo-intense signal on T1-weighted pulse sequences with appreciable signs of contrast enhancement after i.v. administration of gadolinium chelate [105].

5.7. Dermoid Cyst

Dermoid cysts result from the congenital inclusion of cutaneous ectoderm. Intracranial dermoid cysts are usually supratentorial midline lesions containing a mix of fat, hair, calcifications and the products of sebaceous glands and desquamation of a keratinized epithelium. Dermoid cysts rarely arise in the CPA, and may be secondary to the caudal extension of a parasellar lesion [17].

At imaging, a dermoid cyst appears as a well-circumscribed fatty round mass with a thick peripheral capsule that may enhance. In case of rupture, the visualisation of fatty T1-hyperintense droplets in the sulci or a fat-fluid level in the ventricles is highly suggestive of the diagnosis.

5.8. Chordoma

Chordomas develop from remnants of the notochord and are located within the midline, near the clivus, from which they can expand into the CPA. Chondroid chordoma is a pathological subtype of chordoma that may arise more laterally in the petrous bone and grow directly in the CPA [106]. With CT, chordomas appear hypoattenuating soft-tissue mass associated with irregular bone erosion of the clivus. At MR imaging, chordomas usually appear as lobulated, large, hyperintense masses on T2w images with septa of low signal intensity. Slight enhancement is present.

5.9. Intra-Axial Tumors with CPA Involvement

Sometimes, an intra-axial or intraventricular tumor can be large enough to invade the CPA or to manifest as a CPA mass. In such a case, the intra-axial origin could almost be impossible to define (Figure 31). Diagnosis is difficult, but subtle signs like narrowing of the cisterns, irregularity of the tumor-brain interface, and edema are helpful.

In this context, the most frequent diagnosis includes: pedunculated brainstem glioma, choroid plexus papilloma, lymphoma, hemangioblastoma, ependymoma, medulloblastoma, and dysembryoplastic neuroepithelial tumor (DNET) [17].

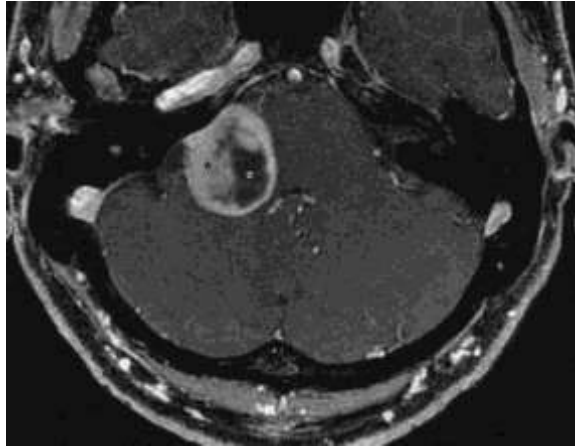


Figure 31. Glioblastoma; axial contrast-enhanced T1-weighted turbo spin echo sequence with fat saturation demonstrating a mostly solid and enhancing lesion (black asterisk) with some cystic / necrotic components (white asterisk) occupying the right CPA. In such a challenging case is not easy to understand the intra-axial exophytic nature of the tumor.

6. TRAUMATIC LESIONS OF THE TEMPORAL BONE

All the bones in our body are the result of an adaptation process [107]. The skull is no exception of what kind of trade-off the evolution process had to face: it must ensure maximum bone strength and resistance to protect its precious content from any external agent while maintaining a lightweight to ensure ease of head movements. A fracture, even considering the age-related physiological variations of our bones, will result when an external force hitting the skull will overcome its intrinsic elastic absorption capacity.

6.1. Temporal Bone Fractures

Nowadays, motor vehicle accidents are the most common cause of trauma. Almost two-thirds of road accidents are associated with head trauma even if the number of sports-, assault- and falls-related head trauma has increased in recent years [108, 109]. In severe head trauma cases, up to 8% of the patients will present a temporal bone fracture; if the patient has a skull fracture the probability that there is also a temporal bone fracture rises up to 22% [110]. Since many pathologic conditions could be associated with a temporal bone trauma a promptly imaging-based diagnosis is mandatory.

Temporal bone fractures can occur with or without brain injuries and are classified within the skull base traumatic lesions as laterobasal fractures.

Taking as reference the long axis of the temporal bone, they are historically classified as longitudinal, transverse (Figure 32) and mixed fractures (Figure 33) [111, 112]. However, this classification result was not always well correlated with the severity of clinical signs and symptoms. A new classification that distinguishes the temporal bone fractures in “otic capsule sparing” and “otic capsule violating” has been proposed (Table 6) [113]. While “otic capsule sparing” fractures are the most common (70-90%), the latter are rare (10-30%) and more

frequently associated with complications such as cerebrospinal fluid leak or fistula, facial nerve injury, hearing loss and intracranial complication such as subarachnoid hemorrhage, epidural hematoma and meningitis [113-116]. A temporal bone fracture can also be classified as petrous or non-petrous [112]. The first, extending to the petrous apex or the otic capsule, is more frequently associated with cerebrospinal leak and facial nerve injury. The latter doesn't involve the petrous apex nor the otic capsule but may extend into the tympanic cavity or mastoid and is more frequently associated with conductive hearing loss [117].

Patients with severe head trauma are often unconscious and, after the emergency room evaluation, are commonly hospitalized in a neurosurgery unit. As soon as the patient's condition allows it, an otological assessment as well as facial nerve evaluation should be performed to facilitate the detection and treatment of potentially correctable middle ear and facial nerve injuries [116].

Table 6. Features commonly associated with “otic capsule sparing” and “otic capsule violating” temporal bone fractures

Features	Kind of fracture	
	<i>Otic capsule sparing</i>	<i>Otic capsule violating</i>
Frequency	Common (70-90%)	relatively rare (10-30%)
Facial nerve injury	rare	frequent (2x)
Risk to develop CSF leak/fistula	low risk	high risk (4x)
Associated profound sensorineural and/or conductive hearing loss	low risk	high risk (7x)
Intracranial complications (subarachnoid hemorrhage, epidural hematoma)	rare	Frequent
Risk for meningitis	low	higher risk throughout life

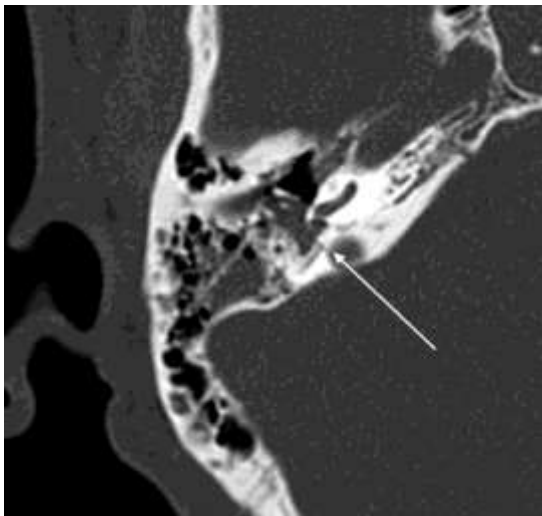


Figure 32. Transverse temporal bone fracture; axial MDCT scan (head trauma spiral CT protocol with 1mm thick slices) shows a transverse fracture line involving the right superior semicircular canal (arrow).

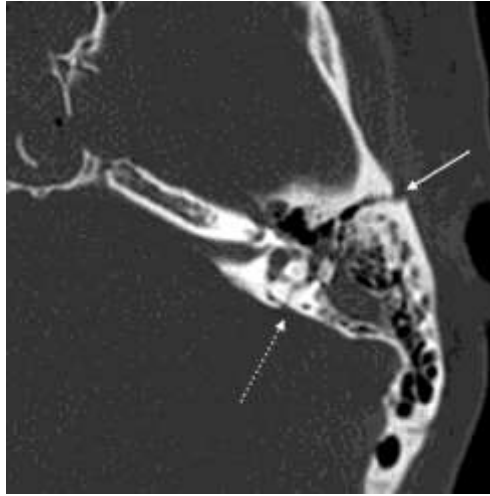


Figure 33. Mixed temporal bone fracture; axial MDCT scan (head trauma spiral CT protocol with 1mm thick slices) shows a longitudinal fracture line involving the left temporal bone pyramid base (arrow) and a transverse fracture line through the ipsilateral inner ear structures (dotted arrow).

A high-resolution CT scan is the first-line imaging examination in patients with severe head trauma with or without suspected temporal bone injuries. On CT images, fracture lines must be differentiated from the so called “pseudofractures.” The latter are normal linear structures very commonly seen on cross-sectional images and are related to the temporal bone anatomy (small canals) and its relationship with adjacent bones (fine sutures) that can mimic temporal bone fractures. If a pseudofracture is suspected, a comparison with the unaffected contralateral side may be helpful in the differential diagnosis. Identifying a small fracture line is not always easy since most polytrauma patients are studied with generic CT trauma protocols (thus slice thickness is rarely less than 1mm as for high resolution temporal bone imaging). If a patient arrives in the Radiology Department with a presumptive diagnosis of temporal bone fracture because of some typical physical findings (i.e., hemotympanum, postauricular ecchymosis and periorbital ecchymosis), an attendant sign of a temporal bone fracture could be the opacifications of mastoid cells, tympanic cavity and external auditory canal with or without blood-fluid levels. More rarely, pneumocephalus as a sign for an open skull base fracture or a brain injury or an extra-axial fluid collection or even small air bubbles in the glenoid fossa of the temporomandibular joint could be indirect signs of a temporal bone fracture [118].

6.2. Ossicular Injuries

Ossicular injuries are usually related to temporal, occipital or parietal region high energy trauma. The ossicular chain is more frequently damaged in longitudinal or mixed fractures of the temporal bone while it is rarely involved in patients with transverse fractures and other kinds of head trauma.

The most common CT finding is the dislocation of the ossicular chain. If an ossicular injury is suspected, multiplanar reconstructions will be helpful to detect the ossicular chain complex; the oval window region should always be carefully evaluated.

Incudo-malleolar and incudo-stapedial joint separation are the most common dislocation injuries; both are best seen on axial slices, the first as a gap between the body of incus and head of malleus and the latter as gap between the body of incus and head of malleus. The whole incudo-malleolar complex dislocation is usually due to an incudo-stapedial joint rupture.

Isolated dislocation of the incus is characterized by the “Y” sign on coronal slices [119] and is far more common than the isolated dislocation of the malleus because of the weaker ligamentary complex.

More rare are the dislocation of the stapes into the vestibulum (stapedio-vestibular dislocation); in these cases, a perilymphatic fistula is often seen and the identification of small air bubbles in the labyrinth could be an indirect sign of it.

Fractures of the single components of the ossicular chain are very rare and hard to identify if high-resolution CT protocols and multiplanar reconstructions are not used.

6.3. Contusio Labyrinthi (Labyrinthine Concussion)

In patients with a negative CT scan for temporal bone fractures but typical clinical signs of inner ear impairment after a head trauma, a traumatic lesion of the inner ear must be suspected. This could occasionally be associated with the opacifications of pneumatized areas of the middle ear in an otherwise negative CT examination. The only oto-neuroradiological examination that could provide a direct demonstration of such an impairment of the inner ear is MRI that could reveal an hyperintense intra-labyrinthine bleeding on T1-weighted sequences (Figure 34) with enhancement on involved inner ear structures on T1-weighted sequences performed after i.v. contrast administration (labyrinthine contusion or concussion). In such cases the risk of fibrosis and ossification of the labyrinth is possible but less frequent than in cases with transverse fractures of the temporal bone [120].

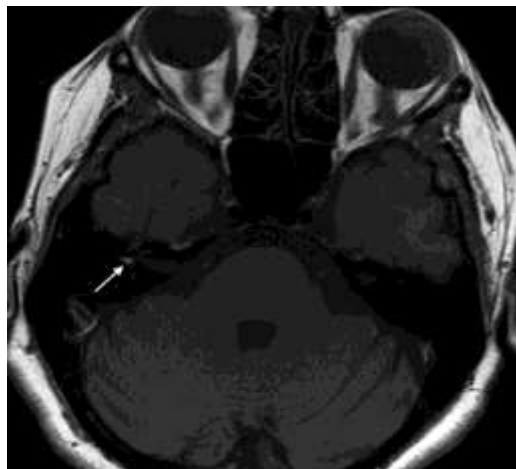


Figure 34. Labyrinthine concussion; axial T1-weighted spin echo sequence shows a small spot of T1 shortening (arrow) due to intra-labyrinthine haemorrhage in a patient with unremarkable CT examination after a head trauma.

6.4. Post Traumatic Hearing Loss

Sensorineural, conductive, or mixed hearing loss may all occur after a head trauma involving the temporal bone. After a trauma, use of a systematic approach to explore the main functional components of auditory pathways is highly suggested [121]. Since conductive hearing loss (CHL) is caused by the impairment of the ossicular chain, high-resolution CT will be the best imaging examination to investigate what part of it has been affected and how (dislocation or fracture). In cases of sensorineural hearing loss (SNHL), high resolution CT scan is still useful to identify indirect signs of inner ear impairment such as pneumolabyrinth and perilymphatic fistula, but it's not useful to detect a labyrinthine haemorrhage (see labyrinthine concussion paragraph) or brain axonal shearing injuries along the central auditory pathways. In these cases MRI is the more exhaustive neuroradiological examination to perform.

6.5. Facial Nerve Injury

Trauma (blunt, penetrating and iatrogenic) is the second most frequent cause of facial palsy; Bell's palsy is the most common and is still a diagnosis of exclusion [122, 123]. Most of the post-traumatic facial nerve injuries are caused by temporal bone fractures. Even if "otic capsule violating" fractures are relatively rare, they are those more commonly associated with facial nerve injury. Blunt trauma usually leads to nerve compression and subsequent edema and contusion. Post traumatic facial nerve transection is very rare. Even if most temporal bone injuries do not require an urgent surgical intervention, it has been demonstrated that in cases with a facial nerve injury, the earlier the facial nerve decompression is performed, the better the chances of a good recovery since bone fragments can prevent axonal regrowth [123]. Brodie and colleagues, analyzing 820 temporal bone fractures, identified the severity and the delay of onset as the two most important prognostic factors in recovery of post-traumatic facial paralysis [124].

To identify a facial nerve injury, the whole course of the nerve must be analyzed. On high resolution CT images, multiplanar reconstruction (MPR) will be extremely helpful for the identification of facial nerve canal post-traumatic lesions. Geniculate ganglion region, either in association with a transverse or an anterior longitudinal fracture, is the most common localization of traumatic facial nerve injury [124]; coronal is the one best plane to identify such a lesion. Lesions of the posterior genu or of the descending branch are commonly associated with a posterior longitudinal fracture; sagittal is the best imaging plane for a correct diagnosis. MRI is more sensible in investigating soft tissues and so is more useful in showing the damaged nerve at any level from the brainstem to the fundus of the internal auditory canal.

6.6. Vascular Injuries (Carotid Canal and Jugular Gulf Impairment)

The complex anatomy that characterizes the skull base and the temporal bone leads to the risk of injury also to vascular structures that pass through and which are in strict contact with nearby bony structures.

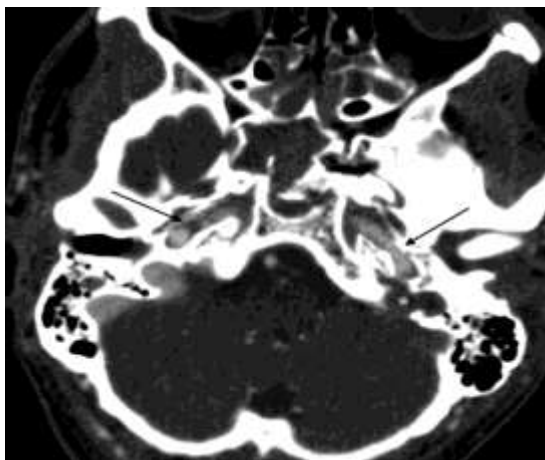


Figure 35. Post-traumatic internal carotid artery impairment; CT angiography (CTA) in a patient with multiple facial skeleton and skull base fractures following a severe head trauma. Both ICA canals are impaired with inhomogeneous intravascular enhancement and abnormal vessel contour of both ICAs (arrows). A brain MRI scan performed a few hours later revealed typical watershed territory stroke signs. Note the filling defect of the left jugular gulf (asterisk) as indirect sign of a post-traumatic traumatic dural venous sinus thrombosis (see Figure 36).

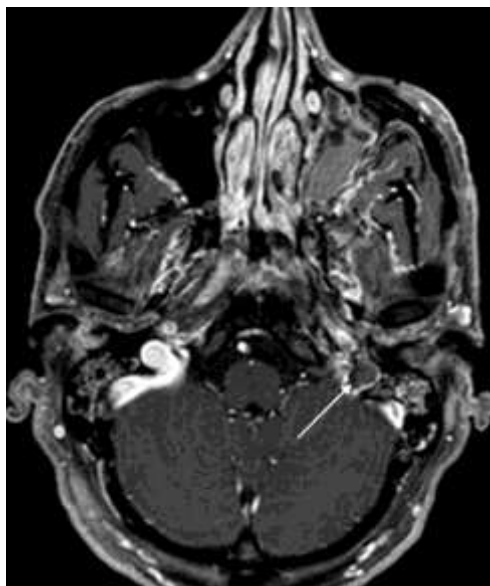


Figure 36. Post-traumatic dural venous sinus thrombosis; axial contrast enhanced T1-weighted turbo field echo sequence (same patient shown in Figure 35) further confirms the left jugular gulf thrombosis: normal enhancing vessel wall surrounding the nonenhancing thrombosed lumen (“delta sign”).

The internal carotid artery (ICA) enters the skull passing through the carotid canal and its petrous segment is located in the petrous part of the temporal bone. The carotid canal should be always carefully evaluated since patients with fractures that extend to it are at an increased risk for carotid artery injury. Complications associated with carotid artery injuries are associated with a worse prognosis and include vessel wall damage (Figure 35) such as dissection, transection or pseudoaneurysm but also complete occlusion and development of

post-traumatic arteriovenous fistulas. CT angiography should be always performed when fractures involving the carotid canal are identified [118]. A brain MRI examination could be helpful to identify vascular brain injuries even in hyper acute phase by the use of Diffusion Weighted pulse sequences.

Veins could be injured after a blunt or penetrating head trauma as well. MDCT venography allowed the identification of traumatic dural venous sinus thrombosis in more than 40% of patients with skull fractures extending to a dural venous sinus or jugular bulb (Figure 36) [125]. Dural venous sinus thrombosis is also one of the unsuspected causes of delayed intracerebral hemorrhage following head trauma with fractures but delayed sinus thrombosis can occur even in the absence of skull fracture [126].

7. PETROUS APEX LESIONS AND OTHER LESIONS OF THE TEMPORAL BONE

Petrous apex lesions are usually an incidental finding while scanning the head with other indications [127]. However, it isn't uncommon that petrous apex lesions presented with nerve palsy, especially of the abducens nerve (6th cranial nerve) due to its proximity to the Dorello canal, next to petroclival fissure. Between the lateral and central skull base, petrous apex is located antero-medially to the inner ear with greater wing of the sphenoid and clivus as medial margins. It is in close relationship with Meckel cave, cavernous sinus, foramen lacerum, Eustachian tube and internal carotid artery (ICA) [128]. CT and MRI are complementary for differential diagnosis [129].

7.1. Leave-Me-Alone Lesions

Leave-me-alone lesions are the most frequent incidental findings and they include asymmetric pneumatization (Figure 37), asymmetric fatty marrow, trapped fluid effusion and variant of petrous apex ossification in the child population. The main imaging characteristic of this type of lesion is the preservation of bone margins and intra-lesion osseous septa. They usually do not require any imaging follow-ups [128, 130].

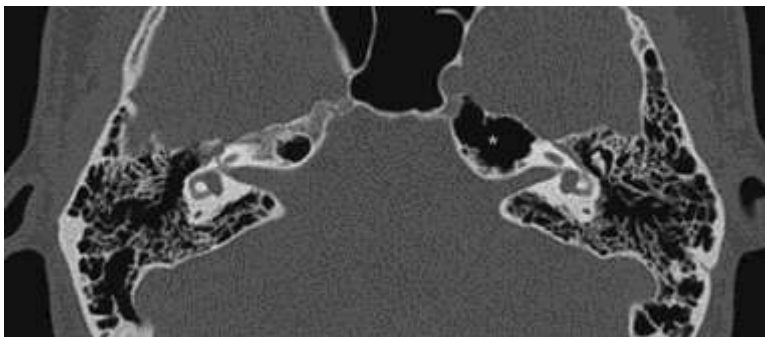


Figure 37. Asymmetric petrous apex pneumatization; axial MDCT scan showing a big air filled cell within the left petrous apex (asterisk).

7.2. Infections and Inflammatory Diseases

In adulthood, leave-me-alone lesions differential diagnosis is mainly represented by cholesterol granuloma (60%). Conversely to asymmetric fatty marrow, cholesterol granuloma is not suppressed with fat-saturation sequences, with a persisting hyperintense signal on T1 and T2 weighted images. Actually, cholesterol crystals are made by hemoglobin catabolism in a long course chronic inflammation process. Rarely does trapped fluid of the petrous apex effusion show slight hyperintensity on T1-weighted imaging due to proteinaceous material; in this case a 2-3 months follow-up imaging is recommended [131]. Mucocoele should be also mentioned as T1-hyperintense petrous apex lesions in relation to its mucoid content, always considering the rarity of the lesions [132].

Trapped fluid effusion is a sterile retained fluid collection in a pneumatized petrous apex, whereas petrous apicitis is a suppurative infection usually extended from severe otomastoiditis or invasive sinusitis (Figure 38). On CT scan, opacification of the petrous air cells has blurred margins and could be combined with demineralization or erosion of the adjacent bone [128]. On MR imaging, fatty marrow has an inhomogeneous signal on T1 and on fat suppressed T2 images. Enhancement is usually intense after i.v. contrast administration, differently from trapped fluid effusion which has thin linear peripheral rim enhancement. Adjacent structures can be involved in uncontrolled infections leading to meningitis, thrombophlebitis or empyema. Nowadays, Gradenigo syndrome (characterized by the triad of suppurative otitis media, pain in the distribution of the trigeminal nerve, and abducens nerve palsy) or complicated petrous apicitis is extremely rare due to the wide use of antibiotics [133].

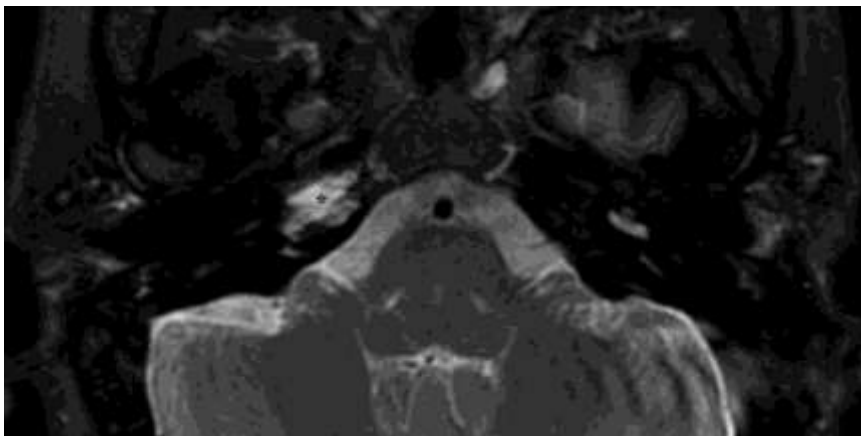


Figure 38. Petrous apicitis; axial T2-weighted turbo spin echo with fat saturation revealing an inhomogeneous fluid collection within the right petrous apex (asterisk).

Pseudotumor is a rare locally aggressive inflammatory disease of the soft tissues adjacent to petrous apex; differential diagnosis based on imaging characteristics is extremely difficult because of its intense enhancement after Gd administration that make it prone to be confused with tumors or invasive infections. Moreover, sometimes it presents bony erosion. A biopsy is necessary for the diagnosis [134].

7.3. Neoplasms

The most frequent neoplastic lesion located at the petrous apex is chondrosarcoma, representing 6% of all skull base tumors. It is a well-differentiated tumor arising from the cartilaginous remnants of the petro-occipital fissure. It can be associated with Ollier disease or Maffucci syndrome and occasionally with Paget disease. A CT scan is extremely useful to assess tumor characteristics because more than 50% of them presented calcifications of the matrix, usually rounded or curvilinear. The margins are lobulated and the adjacent bone is not sclerotic. On MRI, chondrosarcoma enhance avidly, whether homogeneously or not. In the differential diagnosis of a lytic enhancing soft-tissue mass centered on petrous apex, it should be considered chordoma that is usually more central located, and rhabdomyosarcoma in childhood population. Ewing sarcoma should also be included even if it is more rare [128, 130].

7.4. Non-Neoplastic Lesions

Fibrous-osseous lesions of the petrous apex are usually expressions of a widespread disease of the skull. Paget is a disease of the aged population, whereas fibrous dysplasia is typical of children and young adults. Fibrous dysplasia can be mono or polyostotic. Even if temporal bone is frequently affected, petrous apex involvement is uncommon. On MR imaging, monostotic disease can mimic malignancies due to avid enhancement after Gd contrast administration. Complications could be caused by foramina narrowing [130]. Aneurysmal bone cyst involving temporal bone is extremely rare. Imaging appearance is similar to aneurysmal bone cyst involving any other osseous structures of the body and is characterized by bubble and multiloculated appearance, which demonstrates fluid-fluid levels and septal contrast enhancement on MR imaging. Histopathological confirmation is needed to exclude giant cell tumor of the bone [135].

Petrous apex is the election site of meningocele in intracranial idiopathic hypertension (IHH), due to chronic increased CSF pulsations. Meningocele area well-defined CSF-filled lesions laterally to the Meckel cave, sometimes containing Gassner ganglion. The treatment depends essentially on the presence of CSF leaks in relation to an extended scalloping of the bone [136]. In children, meningoceles located at the petrous apex combine usually with sphenoid wing aplasia in NF1 [137].

Petrous internal carotid artery aneurysms are mainly asymptomatic, so they are recognized as incidental expanding lesions of the petrous apex with smooth margins and no bony erosion. CTA or MRA is required for the diagnosis [128].

Cholesteatoma is the second most frequent petrous apex lesion after cholesterol granuloma; it can be congenital or acquired, respectively arising from epithelial remnants in petrous apex (congenital) or spreading from tympanomastoid region (acquired). Imaging characteristics of cholesteatoma are the same all over the temporal bone region (see Paragraph 3.3) [138].

7.5. Other Lesions of the Temporal Bone

There are multiple pathological conditions affecting temporal bone not only at the petrous apex but also the temporal squama, the mastoid or the otic capsule. The main differential diagnosis is between tumoral or non-tumoral lesions.

7.5.1. Tumor-Like Lesions

Epidermoid or dermoid cysts are typically located at CPA, as extra-axial intradural masses; rarely can they have an intradiploic location all over the skull (0.25% of all intracranial tumors), also affecting the temporal squama [139].

Acquired cholesteatoma usually affects the structures around the tympanic cavity; congenital origin of the lesion should be considered when an isolated mass is noted above the labyrinthine compartment or in the mastoid [140].

Cavitating otosclerosis could be mentioned as a tumor-like lesion when presenting as a focal well-circumscribed mass. Representing an inactive foci of cochlear otosclerosis, it has a fluid-filled cystic MR appearance, anteriorly located to the IAC or in the pericochlear region. If it is associated with enhancing areas after Gd administration, it should be a mixed active and inactive otosclerosis focus and differentiated from more aggressive lytic lesions (i.e.: metastasis) [141].

7.5.2. Tumors

Temporal bone paragangliomas, Fisch's classification is based on tumor location and is strictly related to surgical management (Table 7) [142]. Paraganglioma is recognized as a locally aggressive highly vascular neuroendocrine tumor with bone, soft tissue and nerve involvement. They can be solitary or multicentric, sporadic or familial. On CT scan, it is usually noted as a lytic lesion near the jugular foramen, except for Class A and B paragangliomas that are limited to tympanic cavity [143]. Typical MR appearance is a salt-and-pepper lesion on T2w sequence, due to intratumoral flow-voids of vascular origin. An angiographic study should be always performed; CT angiography (CTA) or contrast enhanced - MR angiography (CE-MRA) demonstrate arterial vascularization of the lesion (Figure 39), because paragangliomas are also visualized in the early phase of the injection. Time of Flight (TOF) imaging is useful to recognize intralesional arterial vessels, if the dimension of the tumor are adequate to allow it. Digital Subtraction Angiography (DSA) should be necessary only in the presurgical stage. Nevertheless, the real extension of the disease is better delineated in the fat sat T1-w imaging acquired after Gd injection; volumetric acquisition is recommended in presurgical MR studies. PET/CT remains the gold-standard imaging for non invasive diagnosis [144, 145].

A differential diagnosis of temporal bone paraganglioma includes other lytic bone destructive lesions such as metastasis, plasmacytoma or endolymphatic sac tumor.

Metastasis can be located everywhere in the temporal bone. Bony destruction and multiple locations in the body are the best clues for diagnosis. If the abnormal growing cells composing the mass are plasma cells, it is called plasmacytoma. Plasmacytoma can be solitary, or as a part of myeloma with different treatment and prognosis. Metastasis and plasmacytoma have similar MRI features, showing an intense enhancing mass with irregular margins. Histopathological confirmation is needed [127].

Table 7. Fish Classification of temporal bone paragangliomas

Class A (glomus tympanicum)	Limited to mesotympanum.
Class B (glomus hypotympanicum)	Limited to hypotympanum, mesotympanum, and mastoid without erosion of jugular bulb.
Class C	Involvement and destruction of infralabyrinthine and apical compartments. Sub- classification by degree of carotid canal erosion: • C1: no invasion of carotid; destruction of jugular bulb/foramen; • C2: invasion of vertical carotid canal between foramen and bend; • C3: invasion along horizontal carotid canal; • C4: invasion of foramen lacerum and along carotid into cavernous sinus.
Class D	Intracranial extension (D _e , extradural; D _i , intradural): • D_{e1}: up to 2cm dural displacement; • D_{e2}: more than 2cm dural displacement; • D_{i1}: up to 2cm intradural extension; • D_{i2}: more than 2cm intradural extension.

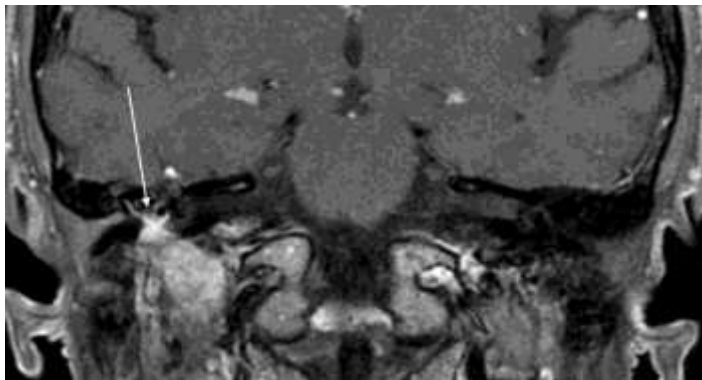


Figure 39. Paraganglioma; coronal MPR from a 3D contrast-enhanced T1-weighted turbo filed echo with fat saturation sequence revealing a lively enhancing lesion in the infralabyrinthine region of the right inner ear (arrow).

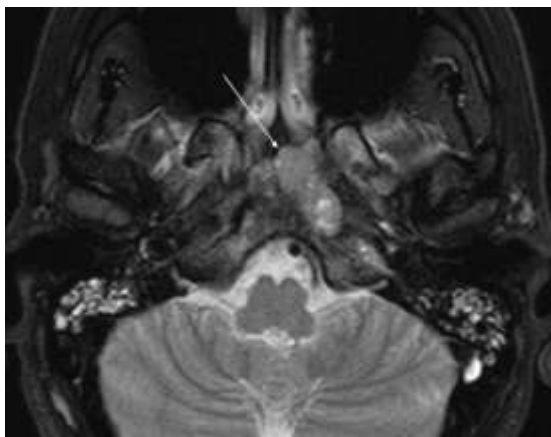


Figure 40. Nasopharyngeal squamous cell carcinoma; axial T2-weighted fast spin echo sequence with fat saturation showing a solid mass (arrow) extending through the pharyngotympanic tube (auditory tube) and infiltrating clivus bone structures with signs of petrous apex involvement (asterisk).

Carcinoma arising from nasopharynx (Figure 40), pinna or EAC could extend into the temporal bone; in relation to the original location of the tumor, they could infiltrate the temporal bone anteriorly or laterally. Conversely, endolymphatic sac tumor is a rare low-grade papillary adenocarcinoma centered on the vestibular aqueduct, eroding through the posterior limit of the temporal bone; it is characterized by spiculae at the erosion margin on CT imaging and T1-shortening areas before Gd administration on MR imaging [145].

Intraosseous meningioma, schwannoma and hemangioma are extremely uncommon. Intraosseous meningioma has a mixed sclerotic and lytic appearance on CT scan and thick meningeal enhancement after Gd administration on MRI. Intraosseous schwannoma are a well-defined lytic lesion, homogeneously enhancing after Gd injection on MRI. Intraosseous hemangioma could have a trabeculated or honeycomb appearance on CT scan and a heterogeneous contrast enhancement, increasing during MRI scanning time [128-131].

8. FACIAL NERVE

The VII cranial nerve (CN VII) contains two distinct roots: a motor root to the muscles of the face and scalp (including platysma, buccinator, stapedius, stylohyoid, and posterior belly of the digastric), and a mixed motor-sensory root to the salivary glands and to taste receptors of the tongue. Facial nerves also carry special visceral efferent motor fibers (SVE). It can be divided in multiple segments [146, 147]:

- 1) Intra-axial segment: the facial nucleus is located antero-laterally in the pontine tegmentum and nerve fibers run postero-laterally, turning around abducens nucleus to exit at the lateral aspect of the ponto-medullary junction. Facial colliculus is a bulge on the IV ventricle floor representing the nerve turn around abducens nucleus, and it is clearly visible on MRI except in cases of nerve hypo/aplasia [148].
- 2) Cisternal segment: on MR high resolution T2w imaging (CISS sequences, see Paragraph 1.2), the cisternal segment is depicted running from ponto-medullary junction to the porus acusticus, crossing CPA anteriorly located to the eighth cranial nerve [147, 149].
- 3) Intra-temporal segment: the seventh cranial nerve crosses the petrous bone entering the IAC and exiting through stylomastoid foramen in the extra-cranial soft tissues [147]. It can be further subdivided in 4 segments:
 - a) Intra-canalicular segment: CISS imaging perfectly resolves IAC content (CN VII-VIII and their divisions); facial nerve is antero-superiorly located in the IAC. At the fundus, it is separated from the inferiorly running cochlear nerve by crista falciformis and from the posteriorly running superior vestibular nerve by Bill's bar, both visible on HRCT scan [149-151].
 - b) Labyrinthine segment: it is the narrowest (<0.7 mm diameter) and shortest part of the bony facial canal running antero-laterally from the fundus to the geniculate fossa, superiorly to the cochlea. Great superficial petrosal nerve (GSPN) is the first facial branch and it exits from the geniculate ganglion carrying the preganglionic parasympathetic fibers of the superior salivary

nucleus through Vidian canal to the pterygopalatine ganglion and then to the lacrimal gland [147, 152].

- c) Tympanic segment: from the geniculate fossa, the nerve makes a 75° turn and runs adjacent to the tympanic cavity directing posteriorly to the second (or posterior) genu. This segment runs inferiorly to the lateral semicircular canal, helpful landmark, and superiorly to the stapes, located immediately before the second genu [149, 153].
 - d) Mastoid segment: at the pyramidal process, the nerve makes a 95°-125° turn (second genu) directing inferiorly to the stylomastoid foramen. The mastoid segment has a vertical orientation, posteriorly to the tympanic cavity. Two branches arise from this segment, stapedius nerve superiorly and chorda tympani inferiorly, respectively carrying motor and special sensory (taste), and parasympathetic (to salivary glands) fibers [147].
- 4) Extracranial segment through the stylomastoid foramen, the nerve enters the parotid glands where it divides in many branches to temporofacial and cervicofacial territories [147].

Table 8. Classification of facial nerve lesions

Aetiology	Lesions	Preferred imaging modality	Distinguishing features
Tumours	Schwannoma	MRI	Enhancing lesions extending into the geniculate ganglion (along the course of the facial nerve).
	Perineural tumor spread	MRI	Extension of a known tumor along the course of facial nerve from mastoid segment.
Infectious	Ramsay Hunt Syndrome	MRI	Abnormal enhancement of facial nerve with classic clinical features (otalgia, vesicles, and facial paralysis).
	Lyme Disease	MRI	Abnormal enhancement of facial nerve with white matter lesions, meningeal enhancement, and classical clinical symptoms (erythema migrans, radiculoneuritis, and arthritis).
Aetiology	Lesions	Preferred imaging modality	Distinguishing features
	Otitis media	CT	Middle ear opacification causing facial nerve canal erosion.
	Cholesteatoma	CT	Middle ear opacification causing facial nerve canal erosion.
Idiopathic	Bell palsy	MRI (atypical cases)	Abnormal facial nerve enhancement with suggestive clinical symptoms.
	Sarcoidosis	MRI	Abnormal facial nerve enhancement with basal cisterns leptomeningeal and dural enhancement.
Traumatic	Temporal bone fracture	CT	Fracture extending to the facial nerve canal.
Vascular	Hemifacial spasm	MRI	Vascular loop at the root exit zone of the facial nerve.
	Hemangioma or venous malformations	MRI/CT	Enhancing lesion at the geniculate ganglion with bony spicules.
Congenital	Moebius	MRI	Absent or hypotrophic facial colliculi, cisternal/intra-canalicular facial segment hypo/aplasia.
	Aberrant course	CT	Variable intra-temporal segments course.
Pontine lesions	Infarct	MRI	Intra-axial T2 hyperintense lesion with diffusion restriction in acute phase.
	Multiple sclerosis	MRI	Multiple T2 hyperintense lesions satisfying revisited McDonald's criteria.
	Cavernous hemangioma	MRI	"Popcorn"-like appearance on T2 with susceptibility artefacts on T2*.

Sensory and parasympathetic components are provided by nervus intermedius (Wrisberg nerve). General visceral efferent parasympathetic motor fibers arise in the superior salivary nucleus and emerge from the ponto-medullary junction as a distinct nerve from facial division. It joins motor root either as it emerges from the ponto-medullary junction or at the meatus of the IAC. Occasionally, it can be depicted by using CISS sequences as a 5th thin nerve along the acoustic canal [146, 149-154].

A small component of general sensory afferent fibers arise from geniculate ganglion to supply trigeminal (CN V₃) innervation of the concha, the EAC and the external surface of the tympanic membrane [146].

The major blood supply of intra-temporal facial nerve is the middle meningeal artery (superficial petrosal and stylomastoid branches), except for the intra-canalicular segment which is in the anterior-inferior cerebellar artery (AICA) territory (labyrinthine branch) [146].

The facial nerve can be affected by many different pathologies (Table 8) [155] resulting in weakness or paralysis and dystonias or spasm [156, 157].

8.1. Facial Paralysis

Depending on which facial nerve segment is involved, different clinical manifestations are recognized. The most critical step is discerning central to peripheral facial palsy. Timing of the onset, patient age and associated symptoms can narrow the differential diagnosis and can guide the choice of the imaging modality and treatment [155-157].

8.1.1. Central Facial Palsy

Among central processes affecting the seventh cranial nerve, cerebrovascular accidents (CVAs) are by far the most frequent [158]. Middle cerebral artery (MCA) or anterior cerebral artery (ACA) stroke can cause contralateral facial paralysis, sometimes sparing the forehead region, in relation to the mixed contra/ipsilateral innervation. Stroke is a time-critical illness and it should be recognized promptly for treatment. Pontine infarcts instead cause an ipsilateral paresis of the face; they usually are lacunar infarcts representing approximately 7% of all ischemic strokes and caused by basilar perforating arteries occlusion. Depending on the blood supplying perforating arteries, pontine infarcts can be distinguished in ventral (anteromedial and anterolateral pontine arteries) and tegmental (short circumferential arteries), with different associated symptoms [159, 160]. MRI with DWI sequence is the gold-standard neuroradiological diagnostic tool for stroke imaging [160].

Brain tumors (primary or metastatic), multiple sclerosis and tumor-like lesions, as cavernous hemangiomas, should be also included as causes of facial central paralysis if located in or by the pons. Whole-brain MRI scan is required in central lesions [147].

However, lesions affecting the facial nerve distal to the decussation in the caudal pons can mimic peripheral facial palsy, despite the lesion etiology [161].

8.1.2. Peripheral Facial Palsy

The most common cause of peripheral facial paralysis is Bell's palsy. Imaging studies are not indicated in the early phase of the disease. If full recovery does not occur after 9 months from the onset, MR imaging is recommended. An earlier imaging study is also indicated if it is associated with other neurological signs or a parotid mass. On MR imaging, abnormal

facial nerve enhancement after Gd administration is present; sometimes, mainly during the acute phase, the nerve is swollen, and it can mimic a schwannoma [162]. If the patient does not progressively recover, follow-up MRI is recommended [163].

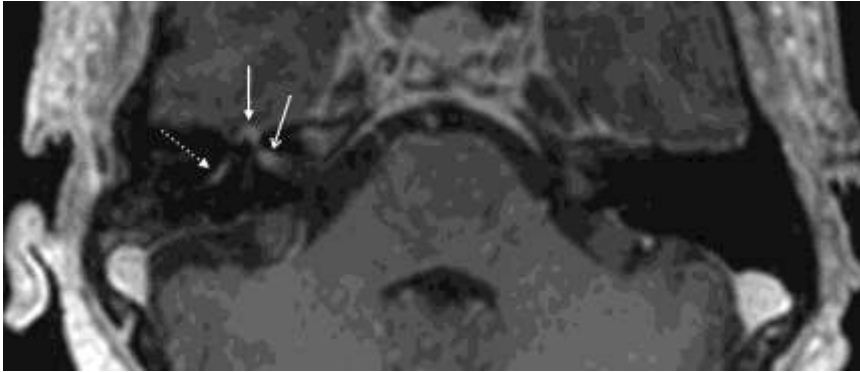


Figure 41. Facial nerve neuritis in a patient with varicella zoster virus reactivation; axial MPR from a 3D T1-weighted fast spoiled gradient echo showing enhancement of the labyrinthine (empty head arrow), tympanic/geniculate ganglion (arrow) and mastoid (dotted arrow) segments of the facial nerve.

Facial nerve enhancement is also present in other inflammatory or infectious diseases that should be included in the imaging-based differential diagnosis checklist even if clinical signs and symptoms should always guide imaging features [150]. Neurosarcoidosis has many different features on a brain MRI, but it is usually characterized by dural and leptomeningeal involvement at the level of basal cisterns, showing bright enhancement after contrast administration [164]. Ramsay Hunt syndrome and Lyme disease are infections of the CNS, respectively caused by Varicella-Zoster virus reactivation (Figure 41) and *Borrelia burgdorferi*. Ramsay Hunt syndrome is usually clinically evident (otalgia, vesicles and facial paralysis), but if MR imaging is acquired, enhancement of the facial nucleus could be observed in association with facial nerve enhancement. Lyme disease is also usually clinically diagnosed, but a whole-brain MRI scan is recommended due to the CNS involvement for that meningoencephalitis [165-167].

Facial nerve enhancement could even be present in facial nerve involvement by pathologies of adjacent structures, such as otitis media, malignant otitis externa, bone fractures or cholesteatoma. Considering that these diseases are used to primarily affect the temporal bone, a CT scan is adequate for the diagnosis [168, 169].

8.1.3. Facial Nerve Tumors

Many different neoplastic processes can affect facial nerves; CN VII schwannomas can affect any portion along the course of the nerve. They usually develop at the geniculate ganglion, but also along the tympanic or mastoid segment. They are well-circumscribed soft tissue masses, scalloping the adjacent bone structure, with avid enhancement after Gd administration except for cystic changes [170]. The most frequent site of origin of hemangiomas is the perigeniculate region, followed by IAC; this kind of lesions arise from the vascular plexus surrounding the facial nerve, and demonstrate a typical CT scan appearance with bony spicules and progressive avid Gd enhancement on MRI as for any venous malformation [170, 171].

Most commonly CN VII is infiltrated or compressed by lesions arising in the IAC (schwannomas, lipomas, choristomas, hemangiomas), in the middle ear (cholesteatomas, adenomas, paragangliomas, paragangliomas), in the parotid (tumors), or in the EAC (carcinomas) [168, 169].

Parotid tumors, especially adenoid cystic carcinoma (70-75%), frequently shows perineural tumoral spread (PTS); on MRI imaging, the facial nerve is swollen, clearly hyperintense on T2 fat saturated sequences due to edema, and avidly enhances after Gd administration. Conversely to inflammatory disease, PTS starts from extra-temporal segment and could eventually cause enlargement of the bony facial canal [172].

8.1.4. Congenital Malformations

Congenital malformation of the facial nerve can be clinically asymptomatic, but in some cases it determines long-standing facial weakness from childhood [148]. In aural atresia, second genu, mastoid segment and stylomastoid foramen can be displaced anteriorly and laterally [173]. Congenital inner ear malformation can be associated with an aberrant course of facial nerve, most frequently the labyrinthine segment (Figure 17), but also tympanic or mastoid depending on the associated malformations, especially of EAC or ossicular chain [152]. In congenital malformations of temporal bone, an HRCT scan is actually always recommended before surgical intervention [174, 175].

Congenital facial paralysis is also caused by abnormalities of facial nucleus in a variety of syndromes, including Moebius, DiGeorge, Goldenhar, Charge, trisomy 13, and trisomy 18. On MR imaging, CISS sequences (see paragraph 1.2) can easily demonstrate the hypo/aplasia of the nerve in the IAC or the brainstem abnormalities [147-150].

Bony dehiscence of the facial nerve usually occurs at the tympanic segment at the oval window level, predisposing the nerve to damaging from inflammatory processes of the middle ear, cholesteatoma or otologic surgery. High resolution CT scan is indicated in these cases [176].

8.2. Facial Dystonias

MR imaging is indicated in hemifacial spasm or twitching to exclude vascular encroaching of the cisternal segment; when a loop of the AICA, PICA, basilar artery or vertebral artery encroaches on the nerve transitional zone (TZ), the result could be an involuntary, unilateral, sudden contraction of facial muscles. The CN VII TZ is the zone of transition between central and peripheral myelination, which is located at 1-2 mm from the brainstem nerve root exit zone (REZ) [1]. Volumetric heavily T2-weighted (CISS) imaging is the gold-standard in demonstrating neural-vascular conflicts. MRI is recommended [147, 170].

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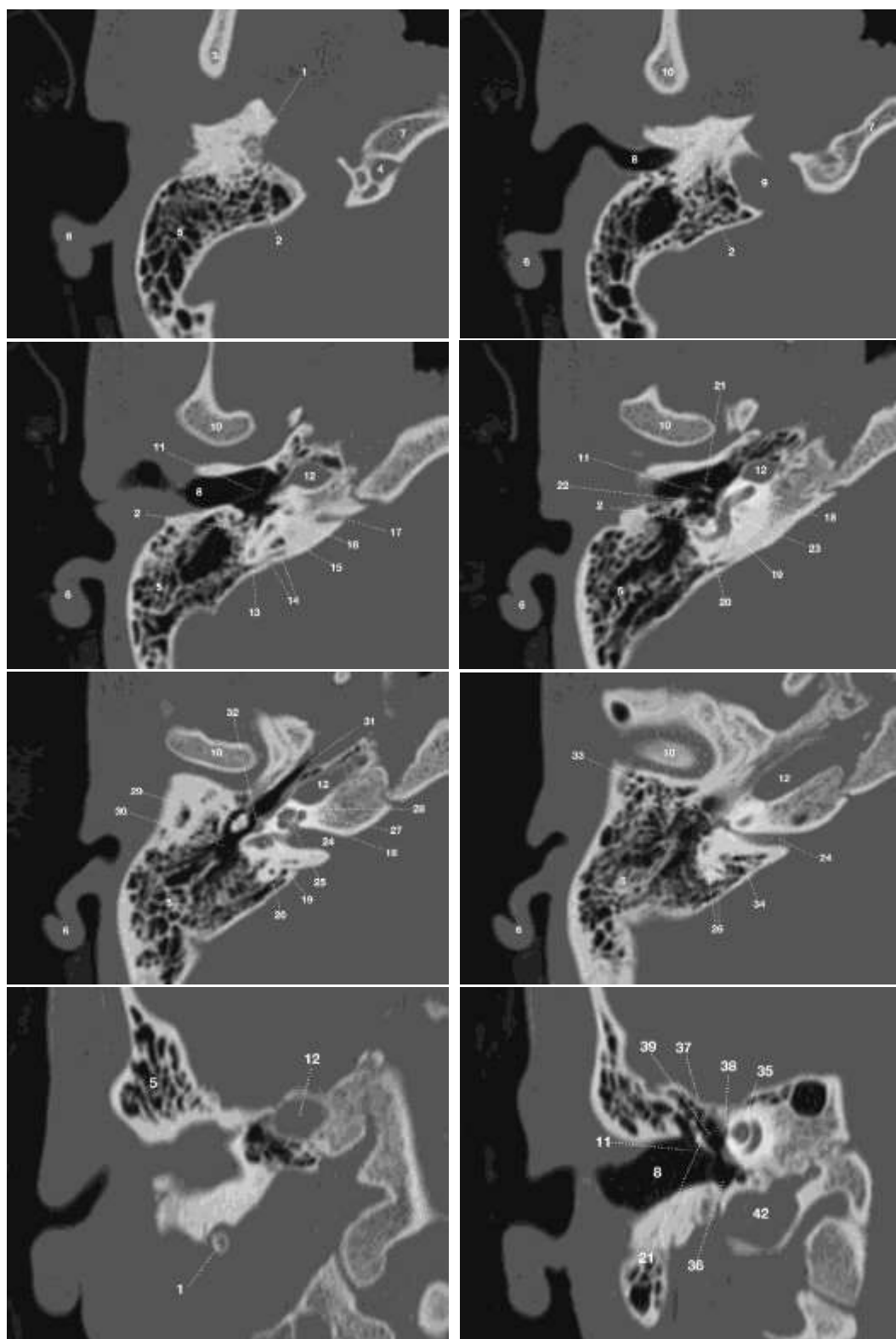
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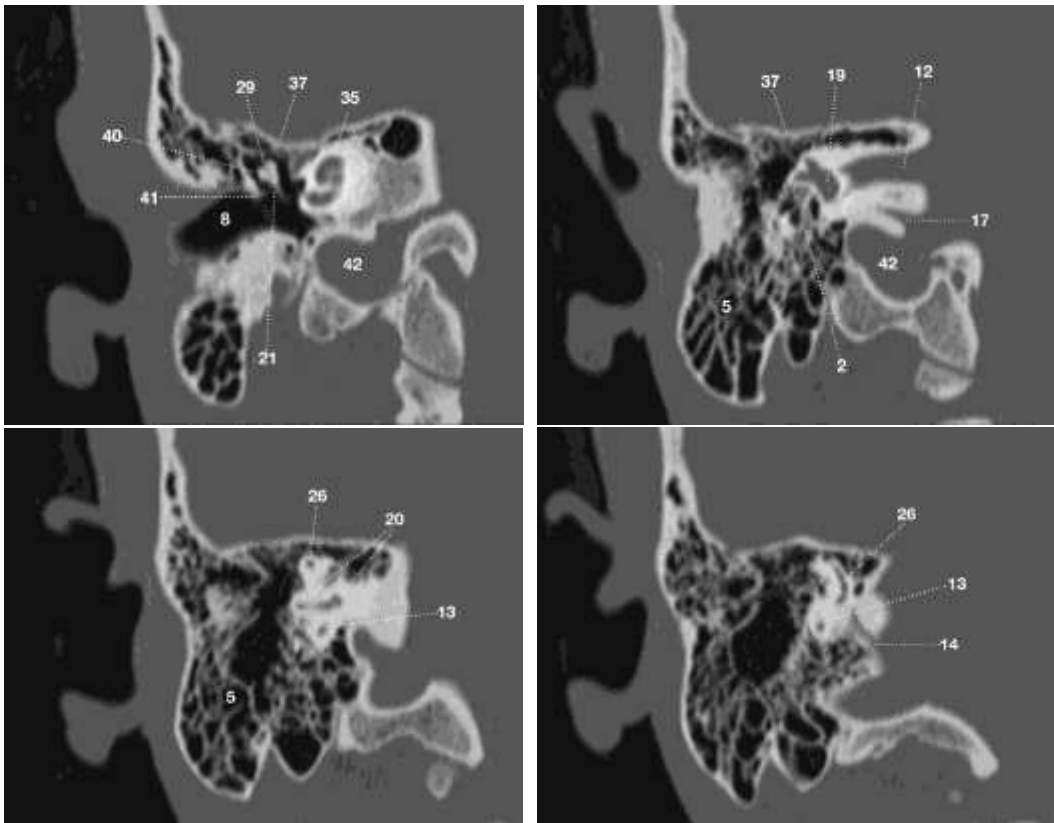
ATLAS

Imaging Based Atlas of the Hearing System

Atlas legend:

- | | |
|---|---|
| 1) styloid process | 22) incus (short process) |
| 2) facial nerve (mastoid segment) | 23) stapes |
| 3) condyloid process | 24) internal auditory channel (IAC) |
| 4) hypoglossal canal | 25) modiolus |
| 5) mastoid cells | 26) superior semicircular canal (SSCC) |
| 6) pinna | 27) middle turn cochlea |
| 7) C1 (atlas) anterior arch | 28) apical turn cochlea |
| 8) external auditory channel (EAC) | 29) incudomalleolar joint |
| 9) jugular foramen | 30) aditus ad antrum |
| 10) condylar process | 31) Eustachian tube entrance |
| 11) tympanic membrane | 32) facial nerve (tympanic segment) |
| 12) internal carotid artery (ICA) | 33) geniculate ganglion |
| 13) posterior semicircular canal (PSCC) | 34) facial nerve (labyrinthine segment) |
| 14) vestibular aqueduct | 35) cochlea |
| 15) sinus tympani | 36) hypo tympanum |
| 16) round window niche | 37) tegmen tympani |
| 17) cochlear aqueduct | 38) tensor tympani muscle |
| 18) basal turn cochlea | 39) tensor tympani tendon |
| 19) vestibule | 40) Prussak's space |
| 20) lateral semicircular canal (LSCC) | 41) scutum |
| 21) malleus | 42) jugular bulb |





Chapter 58

AGE-RELATED HEARING LOSS

***Rocco Bruno, MD, Bruno Galletti, MD, Pietro Abita, MD,
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ABSTRACT

Age-related hearing loss (ARHL, also known as presbycusis) is a hearing loss linked to ageing in which there is a typical deterioration in the ability to understand verbal messages, caused by physiological ageing processes of the whole auditory system, from the peripheral receptors up to the central processing centres (Central Auditory Processing, CAP).

This chronic health condition affects approximately one-third of the population. The incidence among the elder patients (over 80 years old) reaches the 80%, and over 90% of hearing loss in the elderly is caused by presbycusis.

ARHL is classically defined as a progressive, bilateral and symmetrical hearing loss primarily observed in the high frequency region, associated with a deterioration in detection, localization of sound and verbal discrimination, especially in a competitive environment (for example, in the presence of background noise).

Four categories of risk factors associated with ARHL were identified in humans: genetic predisposition, environment, health co-morbidities and cochlear and CAP ageing. For these reasons ARHL can be defined as a multifactorial disorder.

By analyzing human temporal bones, it could be distinguished six distinct forms of ARHL, with different pathologic changes correlated with a different audiologic pattern. According to this classification presbycusis can be divided into: Sensory presbycusis, Neural presbycusis, Strial presbycusis, Cochlear conductive presbycusis, Indeterminate presbycusis, Mixed presbycusis.

This chapter aims to give an overview of the scientific findings related to Age-related hearing impairment that is a complex disorder.

Keywords: age related hearing loss, presbycusis, hearing impairment

DEFINITION

Age-related hearing loss (ARHL, also known as presbycusis) is a hearing loss linked to ageing in which there is a typical deterioration in the ability to understand verbal messages, caused by physiological ageing processes of the whole auditory system, from the peripheral receptors up to the central processing centres (Central Auditory Processing, CAP).

It is defined as a progressive, bilateral and symmetrical hearing loss primarily observed in the high frequency region, associated with a deterioration in detection, localization of sound and verbal discrimination, especially in a competitive environment (for example, in the presence of background noise)^[1].

EPIDEMIOLOGY

AHRI is a chronic health condition that affects approximately one-third of the population. The incidence among the elder patients (over 80 years old) reaches the 80%, and over 90% of hearing loss in the elderly is caused by presbycusis^[2]. The alteration in perception of pure tones already occurs in younger adults (approx. 30 years old), involving the acute frequencies (>10 kHz), which are not commonly examined in the classical tonal audiometric examination. This leads to the idea that a damage in perception of high frequency sounds has already taken place once the diagnosis of ARHL has been made with a conventional pure tone audiometry^[3].

Epidemiological studies have confirmed two kinds of modifications in the auditory thresholds, involving different parts of the spectral frequencies: the decline in the higher frequencies (6-12,5 kHz) seems to have an early outset (beginning even at 31 years old) and a rapid growth while for the low and middle frequencies (up to 4kHz) the decline seems to have a late outset and a slower growth^[4, 5].

The elaboration of data taken by the National Health and Nutrition Examination Survey (NHANES) demonstrates that the prevalence of ARHL is two times higher in men compared to women for frequencies between 0,5-8 kHz, especially after 50 years old, probably because of the protective role played by female hormones. From the same study emerged that in black individuals the prevalence of ARHL is lower than the one registered for white individuals, suggesting a protective role played by melanocyte function. Further studies are necessary to confirm this link, tough [3, 5].

CAUSES AND RISK FACTORS

ARHL is an inevitable hearing impairment associated with reduction of communicative skills related to ageing. Even if the development of this pathology is, as remarked before, inevitable, many Authors have found factors that can affect the extent of hearing loss.

Yamasoba et al.^[6] identified four categories of risk factors associated with ARHL in humans: genetic predisposition, environment, health co-morbidities and cochlear and CAP ageing. For these reasons ARHL can be defined ad a multifactorial disorder.

1. Genetics

Contributions of the genetic factors to ARHL in humans have been well documented, despite the genetic mechanisms underlying the development of this pathology are not yet fully known.

Genome wide association studies have reported a strong link between ARHL and single nucleotide polymorphisms (SNPs) located in GRM7, a gene encoding metabotropic glutamate receptor type 7 protein (mGluR7) [7, 8].

A number of genes and mutations responsible for monogenic non-syndromic hearing loss are linked to ARHL, including: SNPs in 13-kb region in the middle of the KCNQ4, a gene which encodes a voltage-gated K-channel found in both outer and inner hair cells of cochlea [9]; 35delG heterozygosis mutation of GJB2, a gene that encodes gap junction proteins expressed in the inner ear (Connexin 26) [10-14]; mutation in GRHL2, a gene that encodes a transcription factor expressed in cells lining cochlear duct [15]; mutation in MYO6, a gene that encodes myosin VI found in inner ear hair cells [16]. It is known that genes that are linked to oxidative stress such as mutant allele (NAT2*6A), an isoform of N-acetyltransferases which encodes metabolism of reactive oxygen species [17, 18] and Glutathione S-transferases (GSTs) which encodes synthesis of glutathione antioxidant enzymes [19] are linked with the development of ARHL.

Furthermore it is necessary to mention, as possible responsible for presbycusis, mutations in mitochondrial DNA (deletion of 4,977bp of mitochondrial DNA and haplogroups U and K of mitochondrial DNA) [20, 21], and genes coding for Apolipoprotein E [22] and Endothelin-1 [23].

All the findings made on human DNA have been sustained over time by the initial discovery of analogous genes and alleles mutated in laboratory animals, especially in mice of the “inbred” strain.

In fact, in some studies on animal models, there have been identified some genes called AHL (age-hearing loss) that seems to contribute to the onset of ARHL: AHL2 on chromosome 5; AHL1, AHL4 and AHL5 on chromosome 10; AHL8 on chromosome 11; AHL3 on chromosome 17; AHL6 on chromosome 18 [24].

2. Environmental Factors

A variety of environmental risk factors such as exposure to industrial chemicals, occupational and recreational noise exposure are reported to be associated with ARHL [25-27]. Synergistic effects of simultaneous exposure to industrial chemicals and noise has a greater effect on ARHL than the impact of either one of the agents acting on its own [28-31].

3. Health Co-Morbidities

Several diseases and drugs have been associated over time with an increased probability of developing ARHL. The best known associations are between ARHL and type 2 diabetes mellitus, cardiovascular diseases, atherosclerosis, smoking, and the use of ototoxic drugs such

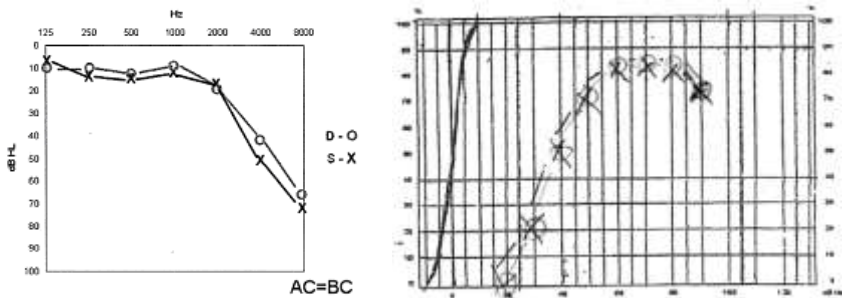
as platinum-derived chemotherapeutics, loop diuretics, anti-inflammatory drugs and aminoglycoside antibiotics [5].

4. Ageing of the Auditory System

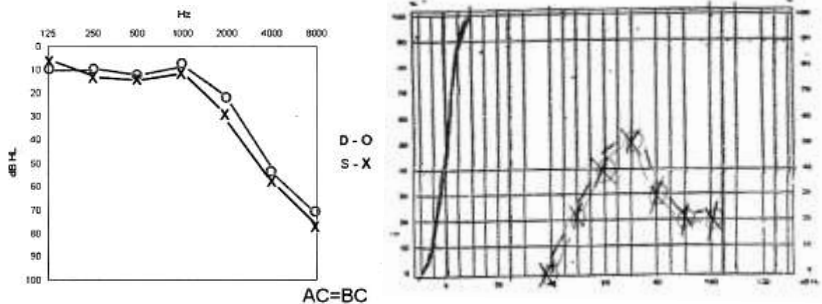
The inner ear is more prone to age-related changes than both the external and middle ear [32].

The first Author who managed to describe the damages caused by ageing on the inner hear, basing his discoveries on underlying case history information, audiometric configurations, and temporal bone analyses, was Harold Friederick Schuknecht [33-36]. He divided ARHL into four distinct classes:

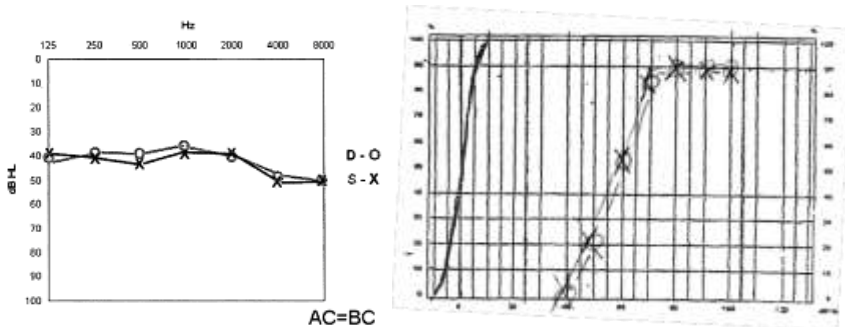
- *Sensory*: loss of hair cells - inner (IHCs) and outer (OHCs) - and supporting cells - rod cells, Deiters, Hensen and Claudius cells. It is distinguished by a sharp drop in the audiometric track on the high frequencies and a bad speech discrimination in noisy environment. The otoacoustic emissions are absent. It is the most common form, typically linked to exposure to noise and environmental factors. It is also called *sociocusis*;



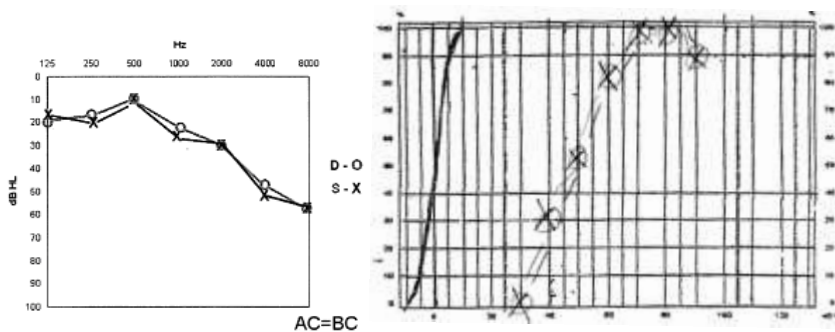
- *Neural*: linked to the loss of afferent neurons of the spiral ganglion, associated with a normal Organ of Corti. The audiogram is distinguished with a falling curve on the high frequencies, typically differentiated from the sensory form due to the bad speech discrimination;



- *Metabolic or strial*: linked to atrophy of cochlear lateral wall and Stria vascularis. The audiogram is characterized by a pantonal hearing loss or with a slight fall on the higher frequencies with a good speech discrimination. The otoacoustic emissions are present. It is thought to be the form strongly correlated to genetic causes, since it is present in about 50% of the sisters, 40% in mother-daughter and about 30% in the siblings;



- *Cochlear conductive*: linked to atrophy and stiffening of the basilar membrane. The audiogram shows a typical and gradual descent on the high frequencies, with good verbal discrimination and with present otoacoustic emissions. It seems to be the least frequent form of the four, less probable from an etiopathogenetic point of view.



Later Shucknecht added two more categories to the four described above:

- *Mixed*: consisting of a mixture of pathological characteristics;
- *Indeterminate*: consisting of none of the aforementioned pathological characteristics.

In spite of the valuable contribution of Schuknecht in defining the pathophysiological mechanisms underlying ARHL, the above classification has been recently overcome due to the difficulties encountered in recognizing the different forms in a strict way. Nowadays it is

common to use a much simpler distinction, based on the anatomical region in which the damage is established: we, then, recognize a *peripheral ARHL* (in which the hearing loss is caused by damages in the peripheral auditory system) and a *central ARHL* (in which hearing problems originate from a CAP dysfunction). The two nosological entities, however, may not present themselves exclusively, acting synergistically in the development of the pathology.

Peripheral ARHL

Peripheral ARHL includes all those forms characterized by an altered morphology of the audiogram with less or none deterioration in speech recognition. These forms are caused by damages to the structures of the inner ear, markedly against outer hair cells (progressive deterioration and decrease in the number of OHCs), stria vascularis (loss of cells and deterioration of its capillaries), spiral ganglion (deterioration of its neurons), lamina spiralis (reduction of the number of nerve fibers at this level) and internal auditory artery (hypertrophy of its elastic lamina) [34, 37-42]. The cause of all these damages has been proven to be oxidative stress: in fact, it has been demonstrated that an increased production of toxic catabolites (following, for example, noise exposure, use of ototoxic drugs, etc.) together with their inadequate disposal (as a result of mitochondrial dysfunction due to ageing) can damage the microstructures of the inner ear causing their death. Even alterations of the cochlear vascularization have been proven to be responsible for the damaging of inner ear's structures [43-53].

As far as we know, there are two different measurable alterations in a cochlea suffering from aging processes: the decrease of the electrical potential of endolymph (due to decreased expression of specific electrolytes transportation enzymes) and the increase in the threshold of the cochlear nerve compound action potential (due to the asynchrony of discharge of the single fibers that compose it [38]).

Central ARHL

Central ARHL includes all those forms in which the main characteristic is an altered speech discrimination together with a partially conserved tonal auditory threshold. These forms originate from an alteration of the cortical networks and connections, resulting in a reduction of cortical plasticity, a physiological phenomenon due to ageing. In central ARHL what is typically altered is the Central Auditory Processing (CAP). CAP dysfunction is indeed occupying more and more importance in the establishment of the late phases of ARHL, while it is thought that the alterations of the peripheral auditory function are the *primum movens* in the development of the initial phases of presbycusis [54-57].

The three fundamental key points analyzed in Literature nowadays are:

4. What kind of alterations we find at various levels of the auditory path and how they affect the perception of complex stimuli, such as speech;
5. If and how these alterations are the effect of a peripheral system depletion, or if and how they run independently of it;
6. If and how there are correlations between ARHL, cognitive impairment and dementia.

I. The main alterations of central processing found in the latest studies are related to three main parameters: deficiency of temporal processing of complex stimuli, lesser ability to encode the signal in presence of noise and decline in spectral resolution. The first of the three seem to be the parameter that contributes most to the deterioration of all those skills useful to understand complex stimuli, such as speech.

As a consequence of aging, in fact, we can find at various levels of the auditory path: a decline in inhibitory neurotransmission mediated by glycine in cochlear nuclei, especially in the dorsal portion, as reported in the strain of aged Fischer-344 rats [58]; a marked decline of GABA-mediated inhibitory impulses together with a prevalence of the excitatory area over the inhibitory one in the inferior colliculus, as reported in various strains of aged rats [59, 60]; a 45% reduction of GABA receptors in the medial geniculate nucleus reported in aged rats [61]; decline in number of SMI-32-immunoreactive neurons and levels of non-phosphorylated neuro-filament proteins [62]. Human studies have found a deterioration in GABA-mediated inhibitory neurotransmission (both presynaptic and post-synaptic) in the primary auditory cortex and a deterioration of the Startle reflex evaluated through pre-pulse inhibition [63-65]. All these changes influence the temporal processing of acoustical stimuli and are reported to be contributing to central ARHL. The alterations of the remaining parameters (decline in spectral resolution and lesser ability to encode the signal in presence of noise) seems to be mainly caused by a deterioration of the capacity of fine tuning of the neuronal populations present in the primary auditory cortex (fine-tuned receptive fields) [66-68]. There is therefore a lower capacity in the primary auditory cortex to execute a fine spectral processing of complex signals, which leads to a lower capacity to encode properly a signal in the presence of background noise (poorly-tuned receptive fields).

It is also thought that age-associated changes in calcium binding proteins (parvalbumin, calbindin, calretinin) disrupt the calcium homeostasis and could lead to impaired synaptic transmission, reduced neural plasticity, and degeneration of neurons reported in ARHL [69-73]. Thanks to the advent of new imaging methods (PET and functional MRI) it was possible to show as a consequence of aging a reduction in both gray and white matter volumes, associated with cortical thinning. Alterations in the above mentioned neural networks are implicated in impaired cognitive functions such as verbal recognition memory, episodic visuospatial memory, learning and association ability, working memory and executive functions as well as attention switching [74-77].

II. An alteration of the central auditory system alone is extremely rare, whilst seems much more common an alteration of both the peripheral and central auditory system at the same time [78]. In addition, it appears that CAP alterations depend also on the reduction of peripheral inputs. (e.g., the deterioration of glycine-mediated neurotransmission at the level of cochlear nuclei found in the Fischer-344 rats [58], the evidence of a tonotopic reorganization of the primary auditory cortex found in animals, which follows the peripheral/cochlear hearing loss) [79, 80]. Even peripheral decline (e.g., different kind of glial alteration found in the strain of C57BL/6J mice) [81] and aging itself (documented as anatomical modifications in the whole brain) have been seen to be responsible for the alterations in CAP [78].

III. Increasing evidence has linked ARHL to more rapid progression of cognitive decline and incidental dementia, in an escalating form that can lead also to Alzheimer's disease (AD) - the most common form of dementia [2, 3, 57]. As far as we know it has not been yet discovered the keystone to explain whether the hearing impairment determines the development of dementia (due to the degradation of sensory inputs sent from the periphery to

the central nervous system) or if cognitive decline leads to an altered capacity of auditory discrimination, especially in noisy environments (leading the elderly to further isolate themselves, worsening their dementia).

From an analysis of epidemiological and clinical evidences, four hypothesis have been theorized to explain the link between ARHL and cognitive impairment [2]:

1. *Cognitive load on perception hypothesis*: cognitive decline may reduce the cognitive resources that are available for auditory perception, increasing the effects of hearing loss;
2. *Degradation of audiological information hypothesis*: when the inputs are poor, either through degraded stimuli (e.g., in noisy environment) or impaired perception, additional cognitive resources are required to understand the signal. Therefore, this cognitive resources will not be available for cognitive roles.
3. *Sensory deprivation hypothesis*: described by Lin and colleagues [82-84], it suggests that hearing loss causes a cognitive decline that is permanent or potentially remediable after rehabilitation (e.g., with the use of hearing aids). It has been theorized that an impaired perception could lead to worsening cognition over time and social isolation, which in turn leads to cognitive decline.
4. *Common cause hypothesis*: according to this hypothesis numerous factors that act synergistically with each other are responsible for cognitive decline in the elderly. These include cardiovascular diseases, diabetes and tissue damage caused by increased Reactive Oxygen Species (ROS) production.

Although none of the four hypotheses is able to clarify the causal link between ARHL and cognitive decline [3], it has emerged that CAP dysfunction can be considered an important and early risk factor in determining the future onset of cognitive impairment up to Alzheimer's dementia [54].

ARHL AND FRAILTY

In addition to the close connection between ARHL and cognitive impairment, ARHL is also considered an important marker for frailty in older age. Frailty reflects a nonspecific state of vulnerability and multisystem physiological change that predisposes an individual to adverse health outcomes such as disability, falls, institutionalization, hospitalization and death [85], and is of high importance in the clinical care of the older population. Thus, psychological, cognitive and social factors contribute to define this condition.

The recruitment of cognitive areas which are not directly responsible for speech encoding causes neural resources to be sacrificed. Alterations in the above mentioned neural networks are implicated in impaired cognitive functions such as verbal recognition memory, episodic visuospatial memory, learning and association ability, working memory and executive functions, and attention switching [3, 54]. Moreover, it is thought that hearing loss is associated with a 20% increased risk of mortality compared with normal hearing [86].

DIAGNOSIS

The most important part in the diagnosis of ARHL is the anamnesis. Investigating the life of the patient, asking if there has ever been a chronic exposition to noise, a genetic susceptibility or a history of chronic illnesses linked to presbycusis, associated with tinnitus (a condition often related to hearing loss) is the cornerstone for a correct diagnosis.

After asking for the medical history it is necessary to submit the patient to different kind of audiological exams, which often have limitations in implementation due to the reduction of the level of attention and cooperation from the patient, which can trigger any anxiety states, further affecting the success of the examination. It will be necessary, therefore, to put the patient at ease, explaining in a clear and comprehensible way each task and the manner in which it must be completed.

During the course of the examinations it is important to take into account that the laxity of the tissues of the auricle and the ear canal, physiological in the elderly, can facilitate, collapsing, a reduction of the auditory acuity [1, 2].

Pure Tone Audiometry

It's the screening test for the evaluation of auditory acuity. It allows to highlight the presence of a hearing loss that is characteristically sensorineural, bilateral and symmetrical with a typical saving of the lower frequencies and a fall on the medium/higher frequencies. The magnitude of this loss depends significantly on the age of the patient and the amount of risk factors present in the medical history.

Speech Audiometry

Speech audiometry refers to procedures that use speech stimuli to assess auditory function. The goal of speech audiometry is to quantify a patient's ability to understand everyday communication. Speech audiometry testing can be done in isolation or with acoustic interferences which can be differentiated into two main groups: a kind of background noise which is similar to the primary signal (e.g., cocktail party) and another kind constituted by pure noise, different from the primary signal (e.g., pink noise).

Results from speech recognition tests in quiet testing condition and in background noise should be evaluated in relation to the pure-tone thresholds. Underperformance in speech recognition in comparison with expectations based on peripheral hearing function suggests central auditory processing dysfunction [54]. If word-recognition scores equal or exceed those that might be expected from the audiogram, then suprathreshold speech recognition ability is thought to be normal for the degree of hearing loss. If word recognition scores are poorer than would be expected, then suprathreshold ability is abnormal for the degree of hearing loss. Abnormal speech recognition is often the result of cochlear distortion or retrocochlear disorder.

The typical pattern of ARHL in speech detection threshold demonstrates what is called "rollover", in which speech recognizing function declines substantially as speech intensity

increases beyond the level producing the maximum performance score. In other words, as speech intensity level increases, performance rises to a maximum level then declines or “rolls over” sharply as intensity increases. This rollover effect is commonly observed when the site of hearing loss is retrocochlear, in the auditory nerve or the auditory pathways in the brainstem [87].

Redundancy and Sensitized Speech Measures (SSM)

There is a great deal of redundancy associated with our ability to hear and process speech communication. Intrinsically, the central auditory nervous system has a rich system of anatomic, physiologic, and biochemical overlap. Among other functions, such intrinsic redundancy permits multisensory processing and simultaneous processing of different auditory signals. Another aspect of intrinsic redundancy is that the nervous system can be altered substantially by neurologic disorder and still maintain its ability to process information. Extrinsically, speech signals contain a wealth of information due to phonetic, phonemic, syntactic, and semantic content and rules. Such extrinsic redundancy allows us to hear only part of a speech segment and still understand what is being said. Extrinsic redundancy increases as the content of the speech signal increases.

The issue of redundancy plays a role in the selection of speech materials. If you are trying to assess the effects of a cochlear hearing impairment on speech perception, then signals that have reduced redundancy should be used. If you are trying to assess the effects of a disorder of the central auditory nervous system on speech perception, the situation becomes more difficult. The solution to assessing central auditory nervous system disorders is to reduce the extrinsic redundancy of the speech information enough to reveal the reduced intrinsic redundancy caused by neurologic disorder [87, 88].

Thanks to the use of sensitized speech measures it is possible to evaluate CAP and any of its dysfunction (CAPD) establishing critical listening conditions, as described above. The most diffused SSM tests in the last few years are based on:

- the administration of phrases with a verbal competitive signal characterized by continuous speech, presented ipsilaterally or contralaterally to the primary signal (SSI-ICM: synthetic sentence identification with ipsilateral competing message, SSI-CCM: synthetic sentence identification with contralateral competing message);
- the administration of phrases in presence of a competitive noise, generally consisting of pink noise (SPIN: speech in noise perception);
- the administration of verbal signal idegraded in its spectral component (“distorted voice”) or temporal component (by introducing interruptions - “interrupted voice” - or compressing the times - “accelerated voice”).

It is not yet clear whether these tests specifically identify CAPD or are significantly influenced by alterations in cognitive abilities, often present in several individuals affected by ARHL with concomitant cognitive impairment, dementia and/or AD (Alzheimer's disease) [89].

Tympanometry

This test provides a valuable aid in the topodiagnosis of ARHL, excluding a transmission deficit in the middle ear (presence of type A tympanograms), and evaluating the presence (with recruitment) or absence of the cocleo-stapedial reflexes [1].

Otoacoustic Emissions

Not necessary for the diagnosis of ARHL in the typical audiological examination. They may be useful in objecting a damage of OHCs in case of peripheral receptor damage [1].

PREVENTION AND REHABILITATION

It is impossible to counteract the aging processes which lead to ARHL. As for the prevention of the pathology it is therefore important to avoid a rapid progression of the deterioration in the auditory system.

As it could be imagined, the main prevention for ARHL is avoiding all those conditions in which the ear can suffer from chronic acoustic stress (e.g., use of headphones and earphones at high volume, attendance of discos, lack of soundproofing in the workplace, exposition to noise in the city environment, hobbies related to auditory stress such as hunting, etc.) and preventing all of those diseases capable of altering the auditory function (ischemic heart disease, strokes, hyperlipidemia, diabetes mellitus, etc.).

The first and fundamental tool of prevention in the diagnosis of ARHL is the periodic control of the auditory function, in order to recognize at an early stage the moment in which the hearing loss begins to determine a deficit in personal and communicative skills of an individual.

There are conflicting opinions concerning therapeutic strategies for ARHL. On the basis of its etiopathogenesis, however, it has been advised the use of substances with antioxidative powers (such as A, B, C, E vitamins, selenium, N-acetylcysteine, methionine, etc.) to contrast the damages made by ROS in the inner ear.

Nowadays the pivotal tool for an early diagnosis of ARHL is still the pure tone audiometry. Every adult over 65 years old should undergo annually to this exam, especially when predisposing factors are documented in his medical history. The main goal of an early diagnosis lies on the possibility to establish a rapid therapeutic-rehabilitative strategy, counteracting the evolution of the pathology and the social isolation, which can eventually lead to cognitive impairment and dementia.

Hearing Aids (HAs) are the most valid and effective instrument in the field of auditory rehabilitation in ARHL. Different studies, in fact, prove that the use of HAs influence significantly in a positive way the quality of life in those who wear them [90]. HAs exploit the functional residues of the organ of Corti amplifying, transducing and sending sounds directly to the tympanic membrane. They can be useful when the hearing loss is not susceptible to medical and/or surgical intervention. For a documentable benefit from the use of HAs there must be an average pure tone threshold higher than 55dB SPL on 500, 1000, 2000 and 4000 frequencies, together with an identification greater than 60% of the words in

closed lists and a recognition of more than 40% of the words in open lists without the help of labiolecture in speech audiometry with an emission of 65dB SPL.

HAs are chosen on the basis of the characteristics of each patient (grade of hearing loss, expectancies and necessities). These modern digital amplification systems are completely innovative and allow, thanks to better sound processing and division of the frequency spectrum into multiple channels, to have excellent results in those hearing losses where personalization and fine adjustment are fundamental for a good hearing rehabilitation.

Clinical trials have demonstrated that hearing loss has a negative impact on working memory, which is important for speech understanding especially in difficult or noisy environments. Other trials proved that the use of hearing aids in the earliest stages of ARHL can improve a person's performances on auditory memory tests [90].

Conventional HAs come in several styles and with a range of functionality. The most common styles of hearing aids are known as behind-the-ear (BTE) and in-the-ear (ITE) hearing aids. A radical change in terms of hearing rehabilitation in ARHL was the birth of Open Fitting (OF) coupling system. Thanks to the OF system the ear is left open and the snail is replaced by a small silicone dome that can be pierced or "tulip-shaped"; it is supported by a small tube that can be empty or more frequently traveled by an electric wire if the receiver is in the ear canal and not in the body of the HA. This has allowed a greater miniaturization and camouflage of the prosthesis, together with a greater tolerability and acceptance by the patient, as well as a better hearing quality thanks to the reduced effects of autophony and occlusion of the external auditory canal [88].

Despite the high incidence of ARHL, the percentage of hearing impaired elderly who use hearing aids is relatively low (it is estimated, in fact, that only 20% of patients who need acoustic amplification regularly use HAs). This is mostly due to cultural and mental status, degree of socialization, education and/or family situation. In this regard, in the context of rehabilitation, a careful counseling activity aimed at patients and their relatives is very important, purposing to encourage the acceptance and adaptation of HAs, encouraging their use. In fact, elderly patients must be gradually educated to amplified hearing, giving them the opportunity to hear again sounds they were no longer used to hear [88].

The main limitation of HAs is in all those severe and profound hearing losses whose gain from the use of HAs is not able to activate the analyzing processes necessary for speech understanding. In these cases, after a careful evaluation of the patient and his life expectancy, and if there are no general medical contraindications, it will be possible to restore hearing thanks to Cochlear Implantation (CI). While in the past CI was not recommended for older patients, to date the outlook has completely changed. In fact, the majority of elderly patients using cochlear implants have demonstrated, both through subjective and objective assessments, a marked improvement in the ability to discriminate speech versus preoperative assessments, as well as an overall satisfaction and better hearing performance even compared to patients who have undergone surgery for CI at a younger age [2, 91, 92].

Given these considerations, counteracting ATHL since the earliest symptoms is very important, both from a prosthetic and an implantological point of view.

Future perspectives in the field of audiological rehabilitation in the elderly are focusing on the possibility of developing a "hybrid" prosthetic system, able to stimulate the ear either by direct acoustic stimulation (as with the HA) or by electromagnetic stimulation (CI). This solution would be particularly indicated in all patients presenting a pure tone threshold rapidly falling on the higher frequencies with partial or total preservation of the lower

frequencies. Other interesting research cues are oriented towards the discovery of one or more drugs able to prevent the death of acoustic receptors, hindering the worsening of ARHL or even exploiting stem cells in order to restore a “physiological hearing” [1, 93].

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Chapter 59

TRAUMATIC SENSORINEURAL HEARING LOSS

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ABSTRACT

Sensorineural hearing loss (SNHL) is a common consequence after head trauma. Head injury may cause temporal bone fracture that can result in damage to the otic capsule, petrous pyramid, and/or other middle and/or inner ear structures. The pathophysiology of hearing loss following temporal bone fractures has been largely attributed to the mechanical forces that grossly disrupt the fragile structures of the middle and inner ear. Another proposed mechanism is endolymphatic hydrop resulting from obstruction of the endolymphatic duct by the temporal bone fracture.

However, remains a subset of patients who had traumatic brain injury with hearing loss without temporal bone fractures. There are different mechanisms that can cause such SNHL: disruption of the membranous labyrinth, avulsion or trauma to the cochlear nerve, interruption of the cochlear blood supply, hemorrhage into cochlea, and perilymphatic fistulae.

Prompt evaluation of patient, early diagnosis and early treatment improves the prognosis. CT can detect pneumolabyrinth and signs of perilymphatic fistulae but fails to detect subtle lesions within the inner ear, such as labyrinthine haemorrhage or localized brain axonal damage along central auditory pathways, which are better detected by MRI.

Treatment can be based upon etiology. If no definitive or treatable etiology is found, treatment is done as in Idiopathic sudden sensorineural hearing loss. Oral corticosteroid therapy is among the few treatment modalities that have gained acceptance. Intratympanic injection of dexamethasone is shown to effectively improve hearing in patients with severe or profound SNHL after treatment failure with standard therapy. Cochlear implants have been demonstrated to be effective in restoring hearing in cases of

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bilateral profound SNHL after traumatic injury, although traumatic and anatomical limitations may make some patients unsuitable for cochlear implantation.

Keywords: sensorineural hearing loss, traumatic sensorineural hearing loss, temporal bone fracture

INTRODUCTION

Head injuries are sustained by 5% of the population annually. Sensorineural hearing loss (SNHL) is very common following traumatic head injury with the incidence ranging from 7% to 50% [1]. Hearing impairment can be due to central or peripheral causes with middle ear or cochlea being the most common site of peripheral injury. The most pronounced injury is fracture of temporal bone but even labyrinthine concussion is frequent [2].

Since the injury occurs to the ear that contains both hearing and vestibular apparatus, generally SNHL is also associated with tinnitus, dizziness or vertigo [3].

In some patients deterioration of hearing and vestibular functions occurs immediately after head injury and it may be transient or permanent. In other patients the symptoms may not manifest until a few weeks post trauma. In some cases patients can show facial nerve palsy or perilymphatic fistula.

A prompt diagnosis is necessary to establish the best treatment and improve the prognosis.

PATHOPHYSIOLOGY

Traumatic brain injuries (TBIs) are leading cause of morbidity and mortality worldwide. TBI is defined as a disruption in normal brain function caused by external forces, either direct or transmitted including falls, motor vehicle collisions, sport-related injuries, abuse/assault, and a strike by a blunt object or pressure blasts [4, 5]. Regardless of its cause, brain injury can result in physical, cognitive and behavioral impairments, leading to temporary or permanent dysfunction [6]. Patients with TBI can appear with significant central and peripheral neurological deficits. Auditory dysfunction after TBI has been well described in literature [7]. In order to better understand the mechanism underlying the traumatic sensorineural hearing loss, TBI can be classified into:

1. TBI with temporal bone fracture
2. TBI without temporal bone fracture

TBI with Temporal Bone Fracture

The temporal bone forms a part of the lateral skull base and houses the hearing and balance organs; it also brings the facial nerve from the brainstem to the facial soft tissues. The bone itself is subdivided into four parts: the mastoid process, the tympanic portion, the squamous and the petrous apex [8]. Temporal bone fractures have traditionally been classified

as either longitudinal, transverse, and/or mixed according to the long axis of the fracture line considering the long axis of the petrous bone (Table 1) [9]. Longitudinal fractures are generally the most common of the two types and result from laterally derived blow. The fracture lines run parallel and extend through the petrosquamous suture line and continue anteriorly to the otic capsule. This results in a haemotympanum and ossicular disruption causing a conductive hearing loss (CHL) in the patient. The facial nerve (FN) could be involved in approximately 15%–20% of these fractures. Transverse skull base fractures are commonly caused by direct trauma delivered to the back of the head. The fracture line begins at the jugular foramen and extends across the petrous pyramid to the area of the foramen spinosum and foramen lacerum. Transverse fractures can lead to SNHL and vertigo. 50% of patients experience facial nerve palsy ¹⁰. Increasing data demonstrate that the majority of these fractures do not fit easily into one these categories but have mixed features.² Moreover, this fracture classification does not provide useful prognostic information with regards to neurotologic deficits [11]. In 1994, a simpler method of classifying fractures proposed by Kelly and Tami [12], is to separate fractures into otic capsule disrupting or otic capsule sparing (Table 1). Their classification has proven more predictive of clinical outcomes [13].

Fractures that disrupt the otic capsule will almost always result in a sensorineural hearing loss (SNHL) and are associated with a much higher incidence of facial nerve paralysis, nerve disruption, cerebrospinal fluid (CSF) leaks, and intracranial complications as compared with otic capsule sparing fractures. Blows to the occipital region usually cause otic capsule disrupting fractures. This kind of fractures runs from the foramen magnum across the petrous pyramid to the otic capsule. They will commonly pass through the jugular foramen, internal auditory canal, and foramen lacerum. These fractures rarely involve the ossicular chain or external auditory canal (EAC).

Otic capsule sparing fractures usually cause a conductive or mixed hearing loss and they are normally caused by a blow to the temporoparietal region and involve the squamous temporal bone and posterosuperior wall of the EAC. They pass through the mastoid air cells and middle ear, fracture the tegmen mastoideum and tegmen tympani, and then continue anterolaterally to fracture the tegmen in the region of the facial hiatus [11].

Table 1. Classification schemes and complications by TBI with temporal bone fracture

Classification scheme	Fracture class	Complications
Traditional classification (In relation to the petrous bone axis)	Longitudinal	Hemotympanum, ossicular disruption, CHL, FN palsy (15-20%)
	Transverse	SNHL, vertigo, FN palsy reported in 50% of patients
	Mixed	Mixed features
Alternative classification (Kelly and Tami, 1994)	Otic capsule disrupting	SNHL, higher incidence of facial nerve paralysis, nerve disruption, CSF fistula, intracranial complications
	Otic capsule sparing	Conductive or mixed hearing loss

There are other pathogenic mechanisms producing SNHL in temporal bone fractures: the cochlear nerve may be avulsed or directly injured by fractures that extend across or along the

internal auditory canal [14, 15]; vascular vasospasm, thrombosis or hemorrhage into the inner ear may result in SNHL [14, 16]; the fracture line may extend across the vestibular aqueduct, resulting in occlusion and secondary endolymphatic hydrop [14, 17].

TBI without Temporal Bone Fracture

While hearing loss following temporal bone fracture is common, few data exist on auditory dysfunction in patients with TBI without temporal bone fracture. Among possible causes are considered trauma to peripheral pathway (labyrinthine concussion) or even direct damage to the central auditory system [18, 19]. Labyrinthine concussion may be described as perceptive deafness and vertigo resulting from a blow to the head without fracture of bony labyrinth capsule. A head injury can lead to either an isolated damage to the otolith organs (vestibular labyrinthine concussion) or injuries to the labyrinth of the inner ear without damage to the otic capsule or intralabyrinthine limiting membranes (cochlear labyrinthine concussion) [20, 21]. The underlying pathology was thought to be due to damage from the acceleration/deceleration forces on the inner ear. The nature of the injury is a tearing or rupture of the sensory cells from their supporting cell attachments on the basilar membrane induced by the excessive displacement of the basilar membrane. In less severe instances, separations of the Hensen cell tight cell junctions at the reticular lamina are created which also leads to an intermixing of cochlear fluids and the eventual loss of sensory cells [22]. It is also speculated that high-pressure waves caused by a blow to the head is directly transmitted to the cochlea by bone conduction [23-25].

Regarding damage to the central auditory system, there are two primary damage categories: injury to the brainstem such as the inferior colliculi [26, 27] and injury to the brain such as temporal bone contusion [28].

Perilymphatic Fistula with Pneumolabyrinth

A perilymphatic fistula (PLF) is an abnormal connection between the inner ear and middle ear or mastoid cavity secondary to a dehiscence in the otic capsule, oval or round window [29]. PLFs typically present with hearing loss and vertigo following head or ear trauma that can mimic many other otolaryngologic entities, such as labyrinthine concussion, traumatic Meniere's and cervical vertigo. Trauma is currently the most common cause of PLF, and can be associated with blunt or penetrating trauma, with or without associated temporal bone fracture [30].

Pneumolabyrinth describes a condition of acute inner ear dysfunction associated with perilymphatic fistula and the presence of air within the labyrinth. Symptoms associated with pneumolabyrinth include acute hearing loss, vertigo and pressure sensation in the affected ear. These symptoms presumably reflect changes in resonance of basilar membrane motion, impaired transduction, and pressure changes within the labyrinth [31]. The pathophysiology of symptoms produced by pneumolabyrinth is due to the presence of air on the ear membrane potential generation. This could be due to entry of air through an apical opening thereby increasing the threshold of the action potential (CAP) of the auditory nerve [31, 32]; perfusion of scala tympani with air causing immediate and drastic decrease of the cochlear

microphonics (CM) and compound action potential with relatively little effect on endocochlear direct current potential (endocochlear potential) [31, 33]; with air perfusion of the scala vestibule, CM potentials were more drastically attenuated than with similar air applied to the scala tympani, suggesting a poorer prognosis with fistula of the oval window compared with that of the round window [31, 34].

DIAGNOSIS

Clinical Evaluation (Table 2)

The otologic evaluation should include inspection of the mastoid prominence for Battle sign, which is an ecchymosis over the mastoid prominence related to emissary vein disruption seen in lateral skull base fractures and, specifically, temporal bone fractures [35].

Table 2. Diagnostic protocol

Diagnostic levels	Examination	
Clinical assessment	History	Past medical history, onset of facial palsy, trauma mechanism, audiological and/or neurological symptoms
	Clinical examination	• Inspection of the mastoid prominence (Battle sign) • Inspection of the ear canal/tympanic membrane
	Cranial nerve examination	• Functional status of the FN
	Auditory testing	• Pure tone and speech audiometry • ABR
	Vestibular testing	• ENG/VNG • Romberg sign, gait ataxia and moving platform posturography
Radiological evaluation	CT	• Temporal bone fractures and ossicular injuries • Perilymphatic fistula
	MRI	• Detection of inner ear hemorrhage • Post-traumatic lesions of the brain parenchyma

The ear canal must be inspected and assessed for the most common findings associated with traumatic brain injuries including tympanic membrane perforation, bloody otorrhea and hemotympanum [9, 35-37]. In temporal bone fractures it is possible to find external ear canal stenosis, brain herniation and fracture of the roof of the EAC.

Traumatic perilymphatic fistula is suspected in cases of cerebrospinal fluid otorrhea. In otic capsule-sparing fractures, the CSF usually leaks through a fracture of the tegmen tympani or mastoidium into the epitympanum, antrum, and mastoid air cell tract. It can present as clear otorrhea if the tympanic membrane is disrupted or as rhinorrhea if the tympanic membrane is intact. In otic capsule-disrupting fractures, CSF will flow from the posterior fossa into the middle ear through the otic capsule.

It is essential that the functional status of the facial nerve have to be recorded as soon as possible during the initial general clinical examination because a nerve injury could lead to a prompt surgical treatment.

Early audiometric testing is recommended for evaluating the baseline post-injury hearing status [38].

TBI can be associated with conductive, sensorineural or mixed hearing loss that can be assessed with a pure tone and a speech audiometry. In otic capsule-violating fractures, severe to profound SNHL can be immediately apparent. Otic capsule- sparing fractures can manifest both sensorineural and conductive hearing loss. Conductive losses are caused by initial hemotympanum or effusion, and permanent deficits are caused by disruption of the ossicular chain, which occurs in approximately 20% of patients [39]. The most common injuries of the ossicular chain include subluxation of the incudo-stapedial (IS) joint (82%), dislocation of the incus (57%), and fracture of the stapes crura (30%) [40]. A subsequent full audiological examination should be performed three to six weeks post-injury, to allow sufficient time for the resolution of haemotympanum, because the presence of middle ear fluid (CSF or blood) results in a conductive loss.

In labyrinthine concussion, sensorineural hearing loss particularly affected high frequencies with recruitment [21]. When present, the most common pattern of hearing loss is similar to that of a noise-induced hearing loss, with a loss that is most apparent at 4 kHz [41, 42].

The use of auditory brain-stem response (ABR) has been reported as the standard to evaluate comatose patients [43]. Indeed the ABR grading system is a sensitive index of brainstem dysfunction and the presence or prolongation of V wave and I-V interwave latency even in one ear is of good prognostic value in the comatosed patient [43]. Also Testing DPOAE may help in detecting sub-clinical injuries to cochlea. Distortion product oto-acoustic emissions assessment at 3000 and 4000 Hz has a higher predictive value in assessing outer hair cell damage [44].

The presence and type of nystagmus should be noted. Electronystagmography/video nystagmography (ENG/VNG) can aid in categorization of vestibular injury. Romberg sign, gait ataxia and moving platform posturography are helpful to quantify balance deficits [45, 46]. The most common type of vertigo associated with head trauma is benign paroxysmal positional vertigo (BPPV). Most post-traumatic vertigo and nystagmus resolve spontaneously in the first 4 to 6 weeks after injury.

Radiological Evaluation (Table 2)

Radiological evaluation is important in patients with post-traumatic hearing loss. The adequacy and selection of the imaging technique with correct interpretation is crucial for diagnosis and prognosis, enabling the selection of the appropriate treatment [47].

Computed Tomography (CT) is the first choice technique and will allow the detection of alterations that cause conductive hearing loss. It allows radiologists to examine the complex anatomy of the temporal bone with sub-millimetric resolution and it is capable of revealing a broad spectrum of ossicular lesions that may not be apparent on clinical findings alone. Virtual otoscopy with 3-D reconstructions of CT images can provide a different view on ossicular chain anomalies in traumatic conditions [48]. In the case of sensorineural hearing

loss, CT can detect pneumolabyrinth and signs of perilymphatic fistulae but fails to detect subtle lesions within the inner ear, such as labyrinthine haemorrhage or localized brain axonal damage along central auditory pathways [49]. In these cases, Magnetic Resonance Imaging (MRI) with 3D-FLAIR acquisition is very important in the detection of inner ear haemorrhage and post-traumatic lesions of the brain parenchyma that may lead to auditory neuropathy.

The potential lesions that cause post-traumatic hearing loss are discussed below and the most suitable radiological examination will be suggested.

Temporal Bone Fractures and Ossicular Injuries

CT is the modality of choice for evaluating temporal bone fractures (Figure 1). The fractures investigated include fracture line's direction (longitudinal, transverse or mixed), the affected portion (fractures that involve the petrous apex and those that spare the petrous apex)⁵⁰ and the otic capsule involvement (otic capsule violating or otic capsule sparing).

One of the most complex spaces of the temporal bone is the middle ear cavity. Within this space resides the ossicular chain constituted by three ossicles - the malleus, the incus, and the stapes - linked together by two articulations: the incudo-malleolar joint and the incudo-stapedial joint. The incus is the heavier ossicle, with a body and two processes of differing length. The body articulates with the head of the malleus, and the short process is directed posterolaterally while the thin long process runs inferiorly in parallel to the malleus handle. Laterally, the tympanic membrane and the malleus handle close the middle ear cavity. The head of the malleus is better observed on the upper axial slices at the incudo-malleolar joint. The lower slices show the lenticular process of the incus articulating with the head of the stapes. This is connected to the footplate via the neck, from which the anterior crus and posterior crus emerge [49].

Ossicular chain disruption is usually seen with longitudinal fractures or otic capsule-sparing fractures of the temporal bone. CT findings of ossicular injury may be difficult to evaluate due to hemotympanum. Ossicular dislocation is more common than ossicular fracture. There are five types of dislocations: incudo-stapedial joint separation, incudo-malleal joint separation, incus dislocation, incudo-malleal complex dislocation, and stapedio-vestibular dislocation [48].

Stapedio-vestibular dislocation is often associated with cochleovestibular symptoms including SNHL, tinnitus and acute vestibulopathy because the injury of the annular ligament or stapes footplate may cause a perilymphatic fistula. Transverse reconstruction of CT in the plane of the oval window and coronal reconstruction can show the medial displacement of the stapes footplate and the distal portion of both stapedial crura within the vestibule due to injury to the annular ligament.

Isolated ossicular fractures are less frequent than joint luxation and may involve any one part of the chain. Injuries to the stapes may be difficult to diagnose at the early stages due to hemotympanum and they are more frequently associated with severe high frequency hearing loss. Fracture of the footplate occurs secondary to a transverse fracture passing through the oval window, and may cause a perilymphatic fistula with pneumolabyrinth [49].

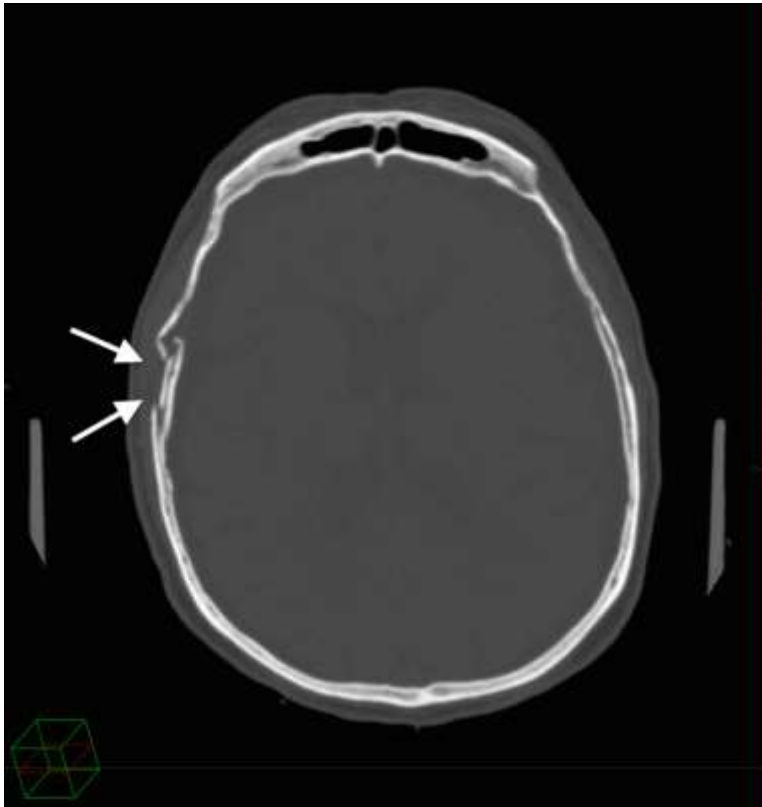


Figure 1. CT scan showing a right temporal bone fracture.

Labyrinthine Concussion

This injury of the membranous labyrinth without bone fracture is difficult to evaluate with CT [47]. MRI can demonstrate hemolabyrinth; in the T1-weighted sequences. It presents as an intrinsic hyperintensity due to its methaemoglobin content [49-53], although the 3D-FLAIR sequence is more useful because of its greater sensitivity to detect subtle changes in the signal of the lymphatic fluid (blood alters the composition of the perilymph) [54]. Non-enhanced FLAIR acquisition may reveal a hypersignal inside the cochlea, vestibule or both [25].

Perilymphatic Fistula

A perilymphatic fistula is a direct connection between the middle ear and inner ear cavities. There are two zones of weakness between these two cavities: the oval window and the round window. The oval window is affected either by a footplate fracture or by a lesion to the annular ligament, which may be isolated or associated with stapedio-vestibular disarticulations or stapes dislocation (external or internal). When the round window is affected, the fracture line can be seen around the edges of the window. The radiologist must

examine CT scan thoroughly to identify the fracture line in the axial and coronal planes [49]. A pneumolabyrinth or pneumocochlea can be seen in the absence of temporal bone fracture [55]. CT can help identify the possible fracture trace and the pneumolabyrinth. Other possible specific signs are the intravestibular displacement of the plate and the presence of opacity at the site of the oval window [56]. When the exact site of bony defect is not identified, CT cisternography with intrathecal contrast can be used. Intrathecal fluorescein is a highly sensitive and specific test used typically when the other methods have failed to locate the fistula. There are occasional reports of neurotoxicity, seizures, and paraparesis, but these complications are infrequent and occur at higher doses of fluorescein than is recommended [11]. MRI can detect perilymph in the middle ear, although it is difficult to differentiate it from the hemotympanum.

Endolymphatic Hydrops

It is a post-traumatic dilatation of the endolymphatic space. In a normal patient, the endolymphatic duct is observed in MRI as a hypointense laminar structure due to its lack of contrast uptake, while the perilymphatic space show contrast uptake and is hyperintense. The saccule and the utricle are individualized and have a rounded shape. To look for a post-traumatic endolymphatic hydrops, it is necessary to perform the FLAIR sequence 4 hours after contrast media injection, to identify a dilatation of the endolymphatic duct that completely obliterates the vestibular ramp and a dilatation of the saccule and the utricle that completely fills the vestibule [47].

Injury to the Central Auditory Pathways

The central auditory pathway should be assessed along its whole length: cochlea, cochlear nerve, cochlear nucleus, inferior colliculus, medial geniculate body and auditory cortex.

It is important to distinguish injuries that occur along the central auditory pathways before the decussation into the superior olivary nucleus that may lead to asymmetrical SNHL, from those potentially responsible for associated auditory neuropathy [57]. The lesions that may lead to SNHL may be secondary to axonal injury, contusion or hemorrhage. Cochlear nerves could be injured by a superficial leptomeningeal hemosiderosis that may be seen after head trauma [58]. The diagnosis of hemosiderosis often relies on MRI with susceptibility-weighted imaging. Theoretically, isolated injury of the thalamus, auditory radiations, or auditory cortex could alter auditory function. Isolation of auditory radiations requires advanced diffusion techniques, such as MR tractography, while the auditory cortex can be visualized with functional MRI [59, 60]. Post-traumatic cerebral contusion located along the Heschl's gyri may be responsible for SNHL. New MR techniques such as susceptibility-weighted imaging or track-weighted imaging will likely prove useful in the assessment of focal brain lesions after trauma, including mild traumatic brain injury.

Labyrinthitis Ossificans

When a temporal bone fracture involves the inner ear structures (usually an otic capsule-violating fracture), labyrinthitis ossificans can result, in which the fluid-filled lumen of the otic capsule is replaced by bone (or fibrous tissue at the early stages) [61, 62]. Clinically, this is associated with profound sensorineural hearing loss and loss of vestibular function. On high-spatial-resolution CT images, osseous attenuation is noted within the inner ear. The corresponding MR images show loss of fluid signal intensity within the membranous labyrinth and enhancement on gadolinium-enhanced images. Heavily T2-weighted high-spatial-resolution sequences are most sensitive for detection at its earliest (fibrous) stage. MR findings precede CT changes by many months, as the earlier fibrous stage prior to ossification may not be detectable on CT images but may be seen on MR images as loss of fluid signal intensity in the membranous labyrinth [63].

TREATMENT

The prognosis for patients with post-traumatic brain injury SNHL is very poor. Cochlear implants (Table 3) have been demonstrated to be effective to restore hearing in cases of bilateral profound SNHL after traumatic injury, given that the functions of the cochlear nerve and brain are intact [64], although traumatic and anatomical limitations may make some patients unsuitable for cochlear implantation.

There are several factors to be considered before performing cochlear implantation in patients with profound hearing loss caused by bilateral temporal bone fractures. The decision to proceed with cochlear implantation after trauma is very difficult and the proper timing of the operation is still controversial.

Temporal bone fracture may result in destruction and degeneration of hair cells, supporting cells, and ganglion cells [65]. It is intuitive that implantation shortly after trauma would provide less time for spiral ganglion cell loss and would increase the chance of successful rehabilitation. On the other hand, surgical intervention that is too early can preclude the opportunity for natural restoration of hearing. Regular audiometric examination must be performed to confirm that the hearing level has been fixed.

In case of labyrinthine concussion, hemorrhage in the inner ear causes a hyperplastic inflammatory response leading to degeneration of neural elements, eventual fibrosis and new bone formation [66]. Labyrinthitis ossificans as a result of TB fractures and secondary infection may also inhibit successful insertion of the electrode array. The most frequent site of ossification appears to be the basal turn of the scala tympani [67, 68]. It is likely that the sooner cochlear implantation is performed after injury, the less time there is for cochlear osteoneogenesis and, therefore, the greater the likelihood for successful electrode insertion. When there is a significant time delay between the initial CT scan and the time of cochlear implantation, repeat imaging is beneficial to rule out labyrinthitis ossificans and other structural abnormalities that may inhibit successful placement of electrodes. Preoperative CT and high-resolution T2 MRI are useful methods to determine the patency of the cochlea [69, 70]. The possibility of retrocochlear lesions (auditory nerve, brain) should be considered. If a patient has bilateral fractures through the internal auditory canal, brain stem implantation (Table 3) may be an option for aural rehabilitation instead of cochlear implantation [71].

Results of cochlear implantation in patients with auditory cortex injuries are equivocal. Cognitive, behavioral and communicative deficits, including aphasia, should all be evaluated to determine the aural rehabilitation method. Promontory stimulation testing can be beneficial to confirm the presence of functioning eighth nerve. Although unilateral cochlear implantation generally provides good speech understanding in quiet conditions, unilateral cochlear implantation patients frequently report difficulties in understanding speech and localizing sound in noisy environments. Bilateral cochlear implantation has several advantages over unilateral implantation including improvement in speech perception in noisy environments and improved sound localization by head shadow, binaural squelch and binaural summation effects. In patients deafened by bilateral temporal bone fractures, bilateral cochlear implantation may be a better method for aural rehabilitation than unilateral cochlear implantation [69, 72].

There is no standard treatment protocol for management of sensorineural hearing loss in the immediate post trauma time [73-76]. Treatment options for SNHL depend on the severity of hearing loss and presence of associated complications.

In case of labyrinthine concussion or otic capsule sparing temporal bone fractures with mild symptoms associated, conservative treatment with high-dose corticosteroids (Table 3) is suggested [9].

Most cases of CSF leak occur in the first week after trauma and close spontaneously with conservative medical management (strict bed rest, elevation of bed by 30°, and avoidance of straining) [63]. If the CSF leak fails to respond, exploratory surgery is suggested. Fat and perichondrium are commonly used for repair [77]. Also temporalis fascia and muscle are used for fistula repair [14]. Repair of the fistula, even if done relatively late, markedly reduces vestibular symptoms and improves low and middle frequency sensorineural hearing.

Table 3. Treatment

Treatment		Indications
Conservative treatment	High-dose corticosteroids	• Labyrinthine concussion • Otic capsule sparing temporal bone fractures • Mild symptoms associated • Incomplete FN paralysis
Early surgical intervention		• FN paralysis • Persisting cerebrospinal fluid leakage • Vestibular symptomatology (with severe symptoms such as intractable nausea and vomiting) • Recurrent meningitis
Aural rehabilitation	• Cochlear implants • Brainstem implantation	• Bilateral profound SNHL after traumatic injury • Possibility of retro-cochlear lesions (auditory nerve, brain)

The indications for early surgical intervention (Table 3) in patients with TBI include facial paralysis, persisting cerebrospinal fluid leakage and vestibular symptomatology (with severe symptoms such as intractable nausea and vomiting), recurrent meningitis [9, 29]. Observation and high- dose steroids can manage incomplete facial paralysis, with surgical exploration considered only if an evident bone fragment is seen impinging the facial nerve

canal. Early complete paralysis may predicate the need for urgent surgical exploration. The perigeniculate area is more susceptible to injury due to traction from the greater superficial petrosal nerve [79-82].

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Chapter 60

ADVANCED OTOSCLEROSIS

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ABSTRACT

Otosclerosis is characterized by a continuous and aberrant process of osteolysis and osteogenesis of the endochondral bone of the otic capsule, most commonly involving the fissula ante fenestram (fenestral otosclerosis) and resulting in a conductive hearing loss. As it undergoes a maturation process, the sclerotic bone may invade deeper into the labyrinth, resulting in retrofenestral otosclerosis and gradually leading to severe mixed hearing loss and then to profound sensorineural hearing loss. This cochlear involvement of otosclerosis audiologically reflects as advanced otosclerosis (AO) and can be defined by audiometric and radiological criteria.

Treatment for AO has evolved over the past 20 years with the improvement in hearing aid devices and the availability of cochlear implants (CI) as an alternative surgical option.

Most authors suggest treating AO with stapes surgery and postoperative amplification by hearing aids.

Cochlear implants have become available in the last 20 years and, since their introduction, many otosclerotic patients have undergone implantation with good hearing and communicative outcomes. Cochlear Implantation in otosclerosis poses some surgical problems, mainly related to cochlear obliteration and facial nerve stimulation. For cases of unsuccessful stapedotomy, the results obtained by a salvage CI are as good as those of CI when no prior stapedectomy was performed.

Keywords: advanced otosclerosis, stapes surgery, stapedectomy, cochlear implantation, CI

INTRODUCTION

Otosclerosis is a rather hereditary disease that usually develops in the post-lingual period, specifically between the second and the fifth decade of life [1]. It is characterized by a continuous and aberrant process of osteolysis and osteogenesis of the endochondral bone of the otic capsule [2, 3]. The most common site of involvement is the fissula ante fenestram (fenestral otosclerosis), which results in conductive hearing loss due to stapes footplate fixation [4, 5]. Hearing loss is initially observed at low frequencies and later also at higher frequencies [6]. As it undergoes a maturation process, the sclerotic bone can increase in size and depth and may invade deeper into the labyrinth, resulting in retrofenestral otosclerosis; this process gradually leads to severe mixed hearing loss and then to profound sensorineural hearing loss (SNHL) [5]. This cochlear involvement of the disease affects about 10% [7] of patients with otosclerosis and, from an audiological point of view, is defined as advanced otosclerosis (AO). Shea et al. [8] estimated that 1.6% of patients with otosclerosis may then evolve to profound SNHL.

DEFINITION

There is no universally accepted definition for advanced otosclerosis. “Far-Advanced Otosclerosis” (FAO) was first described by House and Sheehy [9] in 1961 and was defined by an air conduction (AC) threshold worse than 85 dB and a bone conduction (BC) threshold beyond the measurement limits of the standard clinical audiometers available at that time. In the modern era, the criteria for diagnosing FAO have considerably changed since the availability of more powerful audiometers with higher detection limits. Merkus et al. [10] have therefore proposed that speech discrimination scores (SDS) are more likely to be used than pure-tone thresholds and the term “far advanced otosclerosis” should be no longer applicable. Some Authors prefer to use the term “advanced otosclerosis” instead of far advanced otosclerosis, and define it as a SNHL with decreased speech recognition abilities or with an AC threshold higher than 85 dB and even a poor/unmeasurable BC threshold [5].

Iurato et al. [11] in 1992 described very far-advanced otosclerosis (VFAO) in patients with undetectable air and bone conduction levels with standard clinical audiometers, resulting in a “blank audiogram.” Calmels and colleagues [12] recently described VFAO as a condition characterized by dissyllabic word discrimination lower than 30% at 70 dB SPL in the best aided condition and a blank audiogram.

PATHOGENESIS

The mechanisms leading to SNHL have been widely studied and many theories have been proposed:

- Siebenmann [13] suggested that *toxic substance released* by the otospongiotic foci into the inner ear fluids could impair the function of the cochlea. These hypothesis

has been corroborated by the findings of electron microscopy, that showed the presence of lysosomes at the margins of the advancing otospongiotic foci [14, 15].

- Ruedi [16] described *venous shunts* between the otospongiotic foci and vessels of the cochlea. It is suspected that these shunts might produce venous congestion, interfering with the normal metabolism of the cochlea, resulting in hypoxia and degeneration of the spiral ligament, hence producing hearing loss.
- *Atrophy and hyalinization of the spiral ligament, and of the stria vascularis* have been found in patients with advanced otosclerosis, but the mechanism that produces them is uncertain [17].
- Linthicum et al. [18, 19] proposed the invasion of the cochlear walls by the otospongiotic foci, causing a narrowing of the lumen of the cochlea and a *distortion of the basilar membrane*, with subsequent inhibition of the traveling wave throughout the rest of the cochlea.
- More recently, some Authors proposed that retrofenestral foci may lead to hearing loss through *disturbance of the ionic homeostasis* of the cochlea by hindering ion recycling and reducing the endocochlear potential [20, 21].

In all probability, more than one of these factors is responsible for the hearing loss in each case. The atrophy and hyalinization, which can be determined by both lytic enzymes and venous shunts, may lead both to a distortion of the basilar membrane and to an alteration of the ionic homeostasis. Detritus caused by the aberrant osteoclastic/osteoblastic activity may also alter the normal composition of perilymphatic fluids by inflammatory reactions mediated by immune complexes or by the sum of several of these factors [17, 18].

RADIOLOGIC DIAGNOSIS AND CLASSIFICATION

If it is still debated the utility of imaging in the diagnosis of otosclerosis, there is no controversy in stating that it is of essential importance when the disease progresses into AO and cochlear implantation is taken into consideration.

High-resolution CT (*HRCT*) scanning is the imaging modality of choice for assessing cochlear involvement of otosclerosis, characteristically manifesting with irregularities of the outline of the otic capsule or with the more specific presence of a lucent area in the normally homogeneously dense otic capsule. This lucent area might be presenting as a focal lucency or with the characteristic double ring/halo sign (pericochlear lucency) [22, 23, 24], emerging when the pericochlear confluent foci surround the cochlear lumen [25, 26]. Besides, HRCT can be used to assess the location and extension of hypodense lesions, helping to quantify the degree of otospongiosis and the severity of disease, which has been demonstrated to be correlated to the degree of sensorineural hearing loss [27]. Finally, HRCT might be used for preoperative evaluation of the patency of the cochlear lumen, which can be obstructed in cases of AO, and of the risk of facial nerve stimulation (FNS). These findings can help the surgeon respectively to be prepared for extra-drilling and to choose a perimodiolar electrode rather than straight electrodes in selected patients [26, 28, 29].

In case of intralabyrinthine involvement, also *MRI* can be performed to explore the cochlear status and evaluate the patency of the cochlear lumen [30], particularly on fast-spin T2-weighted scans [31], demonstrated to be even superior to CT scans in the assessment of luminal patency [32]. In cochlear otosclerosis a ring with an isointense signal is usually detected in the peri-cochlear and peri-labyrinthine area on T1-weighted images, with mild to moderate enhancement after gadolinium, related to hypervascularity and inflammatory response in cases of large otospongiotic peri-cochlear foci [31]. T2-weighted images might detect hyperintense signal as well [30, 33]. Lombardo et al. [34] demonstrated three-dimensional fluid attenuation inversion recovery sequence using 3T MRI to be useful for the demonstration of an alteration in the composition of the endocochlear fluid due to inflammation and blood-labyrinth barrier breakdown, which was demonstrated in 81,8% of their patients.

Single-photon emission computed tomography (*SPECT*) using 99-technetium-diphosphonates was proposed by Berrettini et al. [33] as a diagnostic alternative in difficult cases and for medical treatment follow-up, with high sensitivity (95.2%) and specificity (96.7%) in identifying otospongiotic foci in the otic capsule.

Many types of *radiographic grading systems* were proposed in order to describe the location and stage of otosclerosis, often in relationship with audiological findings. Valvassori [22] was the first to propose a grading system for advanced otosclerosis based on disease progression. In more recent studies, Rotteveel and colleagues [26] (Table 1), Symons and Fanning [35] (Table 2) and Kabbara and colleagues [36] (Table 3) described other classification systems based on CT evaluation of the otic capsule involvement.

Table 1. Rotteveel et al. imaging-based grading system [26]

	Otosclerotic Lesions of the Otic Capsule
Type 1	Solely fenestral involvement
Type 2	Retrofenestral (with or without fenestral involvement)
a	Double ring effect
b	Narrowed basal turn
c	Double ring effect and narrowed basal turn
Type 3	Severe retrofenestral involvement (unrecognizable otic capsule), with or without fenestral involvement

Table 2. Symons and Fanning's imaging-based grading system [35]

	Plaques Location
Grade 1	Solely fenestral involvement (spongiotic/sclerotic)
Grade 2	Patchy localized cochlear disease (with or without fenestral involvement)
a	To basal cochlear turn
b	To middle/apical turn
c	Both
Grade 3	Diffuse confluent cochlear involvement (with or without fenestral involvement)

Table 3. Kabbara's imaging-based grading system [36]

	Otosclerotic Lesions
Stage 1	Limited footplate and pericochlear lesions without endosteum involvement
Stage 2	Significant pericochlear and endosteum involvement
Stage 3	Full obliteration of the round window and/or basal turn ossification associated with pericochlear lesions

Table 4. Diagnostic clues suggested by Sheehy (1978) for advanced otosclerosis [37]

(1) positive family history for otosclerosis
(2) progressive hearing loss beginning in early adult life
(3) paracusis during the early stage of the disease
(4) past use of a bone-conduction hearing aid
(5) previous audiograms showing an airborne gap

Although the diagnostic clues suggested by Sheehy [37] (Table 4) together with instrumental imaging may help, definitive diagnosis often requires exploratory surgery [38].

TREATMENT STRATEGIES

The management of patients with AO is a real challenge. Although various methods have been used in recent years, no standard guidelines have been established. The following therapeutic options are in common use [10, 39, 40]:

- A. No intervention and hearing aids with follow-up;
- B. Stapes surgery and hearing aids;
- C. Cochlear implantation;
- D. Direct acoustic cochlear stimulation implant.

In some cases, choosing between these options can be difficult for two main factors: first, with mixed hearing loss it is not easy to predict the success rate of stapedectomy; second, otospongiotic foci around the otic capsule can lead to surgical complications and difficulties during cochlear implantation.

Hearing Aids and Follow-Up

This option can be taken into consideration in case of patients with good audiological (SDS >50%) and radiologic (Rotteveel grade 1, 2A or 2B) findings but with an air-bone gap lower than 30 dB, in which a stapes surgery would be ineffective, considering the reduced conductive component [10].

Stapes Surgery and Hearing Aids

Patients with advanced otosclerosis and no benefit from a powerful hearing aid may be suitable candidates for stapes surgery.

This indication was first discussed by House in 1960 [41]. In 1964 Sheehy stated that “there is no maximum bone conduction threshold above which stapedectomy is contraindicated” [37].

Conducting a stapedectomy with subsequent placement of a hearing aid has been widely studied, with varying audiological results: 46–100% hearing improvement, 38–75% post-operative SDS and 17–75% improvement of SDS [8, 10–12, 37, 38] (Table 5). Several Authors have stated that there are no contraindications for performing stapedectomy in any case of AO and assert that stapes surgery should be considered as first line therapy in these patients, especially in countries with limited economic resources, since even though the results should be unsatisfactory, a contralateral stapedotomy [42] or a salvage CI [6] can still be performed. Abdurehim and colleagues in their meta-analysis [3] revealed that previously failed stapedotomy does not affect the outcomes in terms of SDS after salvage CI.

Complications in patients with advanced otosclerosis are statistically different from those in patients without AO [43]. One of the most feared complications of stapedectomy is the deterioration of sensorineural hearing loss, which can be due to several causes (among them penetration of the prosthesis into the inner ear, perilymphatic fistula or granuloma) and might thus result in a functionally deaf ear. However, the surgeon should not be excessively worried about this possibility in case of advanced otosclerosis, because he is dealing with a severe to profound HL. Furthermore, the ‘second chance’ of CI is still possible.

Some of the *advantages* of stapedotomy are lower cost and difficulties, local anaesthesia, fewer risks and postoperative requirements (fitting of a hearing aid) and better natural sound and music perception. However, stapedectomy does not treat the sensorineural component of mixed hearing loss and does not stop the aberrant maturation process of the otic capsule. Moreover, the outcomes are less predictable, especially if compared with CI [38]. Several Authors have tried to demonstrate the utility of different prognostic factors: it has been stated that patients with severe retrofenestral involvement and speech recognition scores of less than 30% are associated with poorer results if compared with subjects with less retrofenestral involvement and speech recognition scores of more than 50% [5]. For this reason patients should be carefully selected and each case must be assessed individually.

Controversy still exists about the possibility to perform a second stapedectomy on the opposite ear [43]. Many Authors believe that there is no real justification for this if the first stapedectomy was successful [43]. Others believe that each patient should be offered the potential benefit of binaural amplification even for a hearing loss of this severity. In conclusion, each decision should be individualized to the single subject and the final decision should be left to the patient after fully considering all the risks and benefits. In case of contralateral stapes surgery is taken into consideration, the normal protocol of delaying of 1 year the second operation for fear of SN deterioration has no reason to exist in AO, because, as already mentioned, we are dealing with patients with severe to profound HL and no apparent cochlear reserve.

Cochlear Implantation

Cochlear implantation was once considered to be contraindicated in patients affected by otosclerosis, because it was generally agreed that the pathologic process led to an inadequate number of neural elements with subsequent reduction of the electric stimulation [44].

The literature has demonstrated that treating advanced otosclerosis with CIs yield satisfactory results. This can be explained by the fact that this pathologic condition mainly affects the lateral wall of the cochlea, resulting in a degeneration of the spiral ligament and stria vascularis, but leaving the fibres of the auditory nerve uninvolved in a first period [45]; even though spiral ganglion cells are involved by the process, they have been demonstrated to be present in a sufficient number (40-85% of normal) [46] for successful electrical stimulation [47], thus not affecting the performance of the implant [24], but implying the need for higher electrical charges [48].

Several publications have reported hearing improvement in 100% of patients submitted to CI [1, 10, 12, 26, 29, 32, 35, 38, 46, 49-51] (Table 5). Moreover, a significant improvement in speech perception (34-94%) was reported after CI in studies that compared pre- and post-operative speech discrimination (SD) scores [1, 12, 29, 38, 50], with an average SDS after implantation of 45-98% [10]. In a study conducted in 2005 [49] our group found similar results, with an average postoperative SD score of 60% (using two-syllable words test) and 83% (using sentences test).

With such a high rate of success (hearing improvement of 100% vs 46-100% of stapedectomy; post-operative SD scores of 45-98% vs 38-75% of stapedectomy; improvement in SD after surgery of 34-94% vs 17-75% of stapedectomy) [10], CI should be considered the treatment of choice for these patients. However, CI undoubtedly present negative aspects. Some disadvantages of cochlear implantation include high cost, challenging programming/rehabilitation and the high rate of difficulties and complications, thus requiring experienced surgeons. Furthermore, because of the progression of otosclerosis, also late postoperative failure of the CI must be taken into account [31]: in this case reprogramming with higher stimulus levels might be required, although this can increase the risk of facial nerve stimulation.

Table 5. Audiological results after stapes surgery and cochlear implantation

	Patients Hearing Improved	Average SDS after surgery	Improvement SDS after surgery
Stapes surgery	46-100%	38-75%	17-75%
CI	100%	45-98%	34-94%
CI: cochlear implantation; SDS: Speech Discrimination Score			

The *surgical technique* is the same than in standard non-otosclerosis patients, with conventional cortical mastoidectomy and posterior tympanotomy, but continuous and aberrant production of bone in the cochlea can determinate several *difficulties* during the procedure:

- The conventional *landmarks* for CI, such as the promontory and round window niche, may be altered due to bony remodelling in otosclerosis patients, thereby making the identification of scala tympani difficult.
- *Round window and basal turn ossification* often occur in FAO, with a reported incidence of 8-89% and 10-60% respectively [10]. Placing a CI electrode in an ossified cochlea is certainly a challenge, however, is not a contraindication and does not affect the audiological results [2, 46]. A number of techniques have been proposed in order to enable full electrode insertion in these patients: in case of fenestral ossification, extra-drilling may be required to detect the lumen of the basal turn [44]; alternatively the cochleostomy can be placed 1-2 mm cranially with scala vestibuli insertion of the electrode [29, 38, 53].
- *Partial insertion or misplacement of the electrode* has been reported in 19% of patients [26, 35, 38]. Partial insertion can be caused by the obliteration of the apical regions of the scala tympani [8]. The evolution of otospongiotic lesions can lead to the creation of osteolytic cavities surrounding the cochlea, which can be confused with the opening of the basal turn, resulting in an electrode misplacement in this false lumen [26, 28] It is also possible that an electrode normally inserted in the basal turn penetrates the cochlear endosteum and enters this false lumen [54].
- It has been demonstrated that 60% of preoperative CT scans does not reveal findings consistent with otosclerosis. Therefore, the surgeon must be prepared for extra-drilling despite lack of imaging findings [32].

In otosclerosis patients CI *complications* have been described more frequently than in non-otosclerosis ones:

- *Facial nerve stimulation (FNS)* has been reported between 25 and 75% [26, 29, 55] of otosclerosis patients versus the 0.9-14.9% of the general CI population [6]. It is thought to occur because of an altered electrical impedance of the spongiotic bone: this can generate current leaks outside the cochlea, especially in case of partial electrode insertion [54-56], thus resulting in an electrical shunt with the facial nerve [25]. The bone resorption and the progressive thinning of the bone between the electrode and the facial nerve may contribute to this shunt [55, 57]. It has been suggested that the electrode design can influence the incidence of FNS, with perimodiolar (modiolar hugging) electrodes demonstrated to be a useful strategy for preventing this problem [58].

When it occurs, FNS usually appears with facial twitching, pain and paraesthesia [59] at the first connection of the CI or after an average time period of 6.8 months after implant activation [60, 61], but an onset as long as 13 years after implantation has been described [31]. Some Authors [35] have speculated that the higher incidence of FNS with straight electrodes could be explained by the fact that these devices have been in situ longer than the newer modiolar hugging electrodes.

It has been also demonstrated that the higher risk of developing FNS interests subjects with grade 3 (Rotteveel grading system) advanced otosclerosis [35]. This suggests that disease severity on CT scanning may predict cases in which FNS is more likely.

Once occurred, FNS can usually be resolved by reprogramming or deactivation of the involved electrodes [25], that usually are the most distal/apical one, the ones in close proximity to the geniculate ganglion and labyrinthine portion of the facial nerve [26, 55]. However, when many electrodes require deactivation, the performance of the CI unavoidably decreases. The “variable-mode programming,” by leaving normal pulses for non-offending electrodes and setting wider pulses for the offending electrodes, may represent the right compromise between audiological performance and FNS solving [61]. Another treatment modality for refractory FNS is the injection of botulinum toxin [62]. Gold and colleagues [62] also reported the benefit of oral fluoride treatment in refractory cases. In some cases, FNS cannot be resolved through the aforementioned modalities and reimplantation may be necessary [25, 63].

- Other non-auditory stimulations were reported in the literature to be more common in patients with otosclerosis submitted to cochlear implantation: *tympenic plexus stimulation* (manifesting as otalgia) and *vestibular structures stimulation* (clinically presenting with dizziness) [64]. Other untoward symptoms described in patients with advanced otosclerosis after CI are *tinnitus*, *headaches* [32, 50] and *throat discomfort* [49]. The treatment in all cases consists in the deactivation of the offending electrodes.
- As otosclerosis progresses, demineralization can cause the formation of cavitation around the cochlea with resultant *perilymphatic gusher* during cochleostomy [36].

Direct Acoustic Cochlear Implant

The direct acoustic cochlear implant (DACI) is a new type of acoustic hearing implant designed for patients with severe to profound mixed hearing loss [65] but not yet approved by US Food and Drug Administration.

DACI transfers acoustic energy directly to the inner ear via an implantable electromagnetic transducer introduced into the oval or round window or in a surgically created ‘third’ window [40]. As a result, pathological outer and middle ear structures of the ear are bypassed and the amplified signal is directly provided to the cochlea. Häusler et al. [40] and Bernhard et al. [66] were the first to describe a DACI device called DACS. The successor of the DACS, the Codacs investigational device, has been demonstrated to be safe and clinically useful in the treatment of patients with severe to profound MHL due to advanced otosclerosis [67].

Several studies have stated that the outcomes in otosclerosis patients with severe to profound hearing loss treated with DACI, in terms of hearing improvement and speech intelligibility, are significantly better than in case of CI [63] or conventional hearing aids [68].

Busch and colleagues [68] defined the indication for DACI as a BC threshold between 40 and 80 dB hearing loss and AC threshold higher than 60-dB hearing loss. Larger clinic trials with this device are however required to reach definitive conclusions [6].

Treatment Strategy and Counselling

Different criteria should be considered when choosing the best treatment strategy, including rate of success, economic criteria and potential complications of each option.

Merkus and colleagues [10] proposed a *treatment algorithm* that can help the surgeon in choosing the best treatment strategy basing on SD rates and CT findings (Figure 1). First, patients are divided into 3 main groups according to their maximum SD scores, using standard speech audiometry (open-set monosyllables) [69]: group 1 SD scores are less than 30%; group 2 SD scores are 30% to 50%, and group 3 SD scores are 50% to 70%.

For group 1 patients (SDS < 30dB), who often suffer from sever SNHL, the most effective treatment has been demonstrated to be cochlear implantation, because stapedectomy does not act on the sensorineural component. Group 2 patients (SDS between 30 and 50%) might be treated with both CI and stapedectomy in relation to their CT scan Rotteveel grade. In case of severe retrofenestral otosclerosis with Rotteveel grade 2C or 3, cochlear implantation is typically recommended, because of the likely progression of cochlear damage that could make CI very difficult in future. In case of less advanced CT lesions (Rotteveel grade 1, 2A or 2B) the air-bone gaps should guide the surgeon: if the ABG is equal or greater than 30 dB, stapedotomy is recommended; if the ABG is less than 30 dB, CI still remains the best option in the Authors’ opinion. Group 3 patients (SD between 50 and 70%) undergo the same management as group 2, except that in case of limited CT cochlear involvement and ABG less than 30 dB hearing aids and follow-up are recommended rather than CI.

Despite this interesting algorithm appears to be a useful to help the surgeon choose the best treatment to perform, retrospective evidence suggests that CT and audiological findings are not sensitive or specific enough to predict the outcomes of stapedotomy [36, 42]. Furthermore, it has been demonstrated that even in patients with a “blank” audiogram (unmeasurable air and bone conduction thresholds) and 0% SD, stapedectomy with a well-fitted hearing aid can still lead to acceptable outcomes in up to 30% of patients [12, 36].

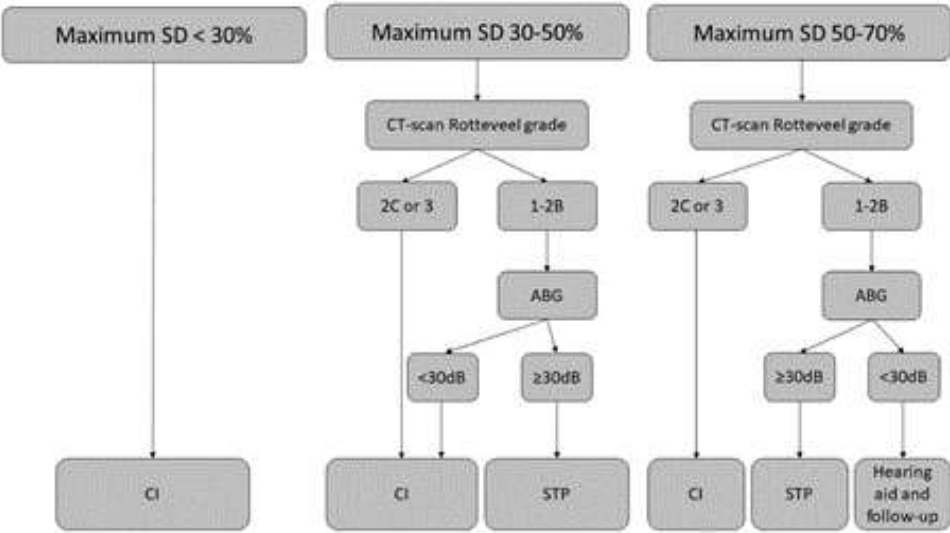


Figure 1. Algorithm guideline proposed by Merkus et al. for advanced otosclerosis. SD: Speech Discrimination; ABG: air-bone gap; CI: cochlear implantation; STP: stapedectomy.

Because of the advantages listed above, several Authors still recommend to consider stapes surgery with hearing aid as a first option [6]. In fact, the results of auditory stimuli appears to be better than electrical stimuli in terms of sound quality, musical appreciation and speech discrimination in loud environments [70-72]. If stapes surgery does not have a successful outcome, a cochlear implantation is still an option [6].

In addition, multiple factors must be considered in the surgical decision, such as the degree of residual hearing in the contralateral ear, the duration of hearing deprivation and the patient preference.

Careful preoperative counselling is extremely important in patients with advanced otosclerosis. Especially in cases selected for stapedectomy, patients must be aware of the risk of the procedure, of the limited goals and of the possibility, in case of failure, that a CI can be carried out in the next future. Failure is normally defined by no improvement of threshold levels or speech recognition with well fitted hearing aids at 3 months after the surgery and when the patient is not satisfied [73]. Nevertheless, patients should be informed that, since cochlear otosclerosis is an evolutive process, the results of a stapedectomy can deteriorate with time; in these cases, CI must be proposed.

Quite recent publications showed promising results with the use of high dose *third-generation bisphosphonates* in the treatment of SNHL in otosclerosis, with stabilization and up to 68% improvement of SD [74, 75]. The mechanism is thought to be linked to a reduction in osteoclast activity and, hence, of TNF-alpha diffusion to the perilymph and hair cells [74, 75]. Although more studies are necessary, this therapeutic option may decrease the number of patients requiring salvage cochlear implantation after stapedotomy and improve the long-term stability of the procedure.

CONCLUSION

Recent reviews concluded that CI leads to a statistically greater and consistent improvement in speech discrimination scores compared with stapes surgery. Stapedotomy is not universally effective; however, it yields results comparable to CI in at least half of patients.

In conclusion, stapedectomy with subsequent hearing aid adaptation should not be forgotten as a valid procedure for these patients. Each case must be thoroughly analysed and the choice of treatment should be individualized for each patient.

For cases of unsuccessful stapedectomy, the option of CI is still open, and the results obtained by a salvage CI are as good as those of CI when no prior stapedotomy was performed.

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Chapter 61

SUDDEN SENSORINEURAL HEARING LOSS

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ABSTRACT

Sudden sensorineural hearing loss (SSNHL), is an important otological disorder that affects up to 5-20 in 100,000 people. It is characterized by a rapid loss of the hearing, usually unilateral, with a sensorineural hearing loss greater than 30 dB over three consecutive frequencies, in less than 72 hours and can be associated with tinnitus and vertigo. It is a real sensorineural emergency that can become a permanent handicap if not adequately treated.

Because of patients recovering rapidly or seeking no medical attention, the true figure might be higher, even if delaying SHL diagnosis and treatment may decrease the effectiveness of treatment. Sudden Hearing Loss can occur at any age but usually affects between 50 and 60 years old and the youngest patients affected are among 20-30 years old. There are not significantly differences in the prevalence between men and women[1-3]. Several pathophysiological mechanisms have been proposed to explain SHL (infective, vascular, and immune disease), but only 10 to 15 percent of the people have an identifiable cause; the majority of cases in fact remain 'idiopathic'[4].

Because no specific cause is identified, the treatments are heterogeneous and can be considered empiric; on one hand therapies' aim is to correct the primary risk factors (smoke, diabetes, hypertension, previous viral or bacterial infections), on the other hand the purpose is to act on the main etiopathogenetic hypotheses (viral infection, immunologic, vascular compromise).

Keywords: sudden hearing loss, sensorineural hearing loss

ETIOLOGY

The etiology of Sudden Hearing Loss (SHL) includes viral/infectious, autoimmune, labyrinthine membrane rupture/trauma, vascular, neurological, and neoplastic causes [5, 6]. Within these broader categories, there are a host of subtypes associated with SHL. An abridged list of recognized causes of SHL is shown in table 1 [7-10].

DIAGNOSTIC EVALUATION

Hearing impairment workup comprehends history, audiometry, tympanometry, including stapedal reflex testing, as well as auditory evoked potentials.

A typical history, per se, often makes for a straightforward diagnosis. In particular, clinicians should focus on the accompanying circumstances, symptom onset and temporal progression, as well as corroborating audiovestibular features (i.e., tinnitus, vertigo/dizziness, aural fullness) [11-13]. Clinically, tinnitus and vertigo affect approximately 77% and 33% of cases, respectively [14-16]. Moreover, the history should include inquiry into prior otologic surgery, exposure to ototoxic agents, viral infections and systemic disorders, such as hypercoagulable states, diabetes and autoimmunity [17-19]. A pure-tone audiometry exam that assesses conventional generated tone frequencies (i.e., 125, 250, 500, 1000, 2000, 4000 and 8000 Hz) is a mainstay of the workup in every patient presenting with SHL, as recommended by the “International Organization for Standardization” (ISO). Furthermore, the clinical utility of the audiogram, together with its morphological features, is not limited to the diagnosis, but rather provides clinician the elements of prognostic value as well (Figure 1).

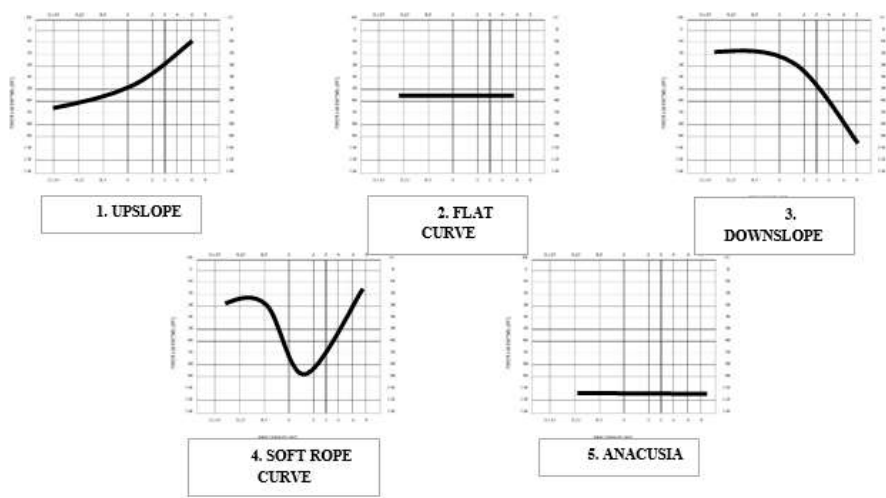


Figure 1. Most common types of curve.

As for the tympanogram and stapedial reflexes, the utility of these assessments mainly lies in the topographic diagnosis of hearing loss. Finally, via objective estimations of electrophysiological hearing thresholds, the hearing impairment workup avails itself of recordings of auditory evoked potentials, which aid in assessing the integrity of discrete constituents of the acoustic-facial bundle and neural circuitry.

Table 1. Causes of SHL

Infectious	Meningococcal men Herpesvirus (simplex, zoster, varicella, cytomegalovirus) Mumps Human immunodeficiency virus Lassa fever Mycoplasma Cryptococcal meningitis Toxoplasmosis Syphilis Rubeola Rubella Human spumaretrovirus
Autoimmune	Autoimmune inner ear disease (AIED) Ulcerative colitis Relapsing polychondritis Lupus erythematosus Polyarteritis nodosa Cogan's syndrome Wegener's granulomatosis
Traumatic	Perilymph fistula Inner ear decompression sickness Temporal bone fracture Inner ear concussion Otologic surgery (stapedectomy) Surgical complication of nonotologic surgery
Vascular	Vascular disease/alteration of microcirculation Vascular disease associated with mitochondriopathy Vertebrobasilar insufficiency Red blood cell deformability Sickle cell disease Cardiopulmonary bypass
Neurologic	Multiple sclerosis Focal pontine ischemia Migraine
Neoplastic	Acoustic neuroma Leukemia Myeloma Metastasis to internal auditory canal Meningeal carcinomatosis Contralateral deafness after acoustic neuroma surgery

PATHOPHYSIOLOGY OF SUDDEN HEARING LOSS

Although a specific cause may be identified in no more than approximately 10% of cases, most available evidence appears to support inflammation and/or hypoxia as the underlying condition(s) leading to cell injury or dysfunction. Accordingly, three main theories have been advanced to interpret idiopathic Sudden Hearing Loss, all of whose hypotheses regarding the pathophysiological mechanisms converge on the common pathway of inflammation and/or hypoxia: vascular, viral and autoimmune theories.

VASCULAR THEORY

Since the inner ear is supplied by terminal blood vessels, the organ is particularly vulnerable to reduced blood flow and/or hypoxic stress. Moreover, the resulting clinical picture closely matches the physiology of the affected area. Unsurprisingly, circulation within the cochleo-vestibular system can be compromised by conditions such as: increases in blood/plasma viscosity; sludging of blood; vasospasm and/or release of vasoactive substances; embolism or thrombosis.

VIRAL THEORY

In 1957, van Dishoeck first advanced a viral theory to elucidate the onset of Sudden Hearing Loss, positing three alternative mechanisms [20] (Figure 2):

1. direct viral invasion of the inner ear or cochlear nerve via the bloodstream, cerebrospinal fluid, or middle ear;
2. reactivation of a latent virus presents in the inner ear: neurotropic viruses sub-clinically infect cochlear neurons, become latent and subsequently are reactivated manifesting as acute cochleitis or neuritis, which lead to sudden deafness;
3. viral antigens stimulating an immune response during a systemic infection induce cross-reacting antibodies (i.e., antigenic mimicry) to antigens of the inner ear.

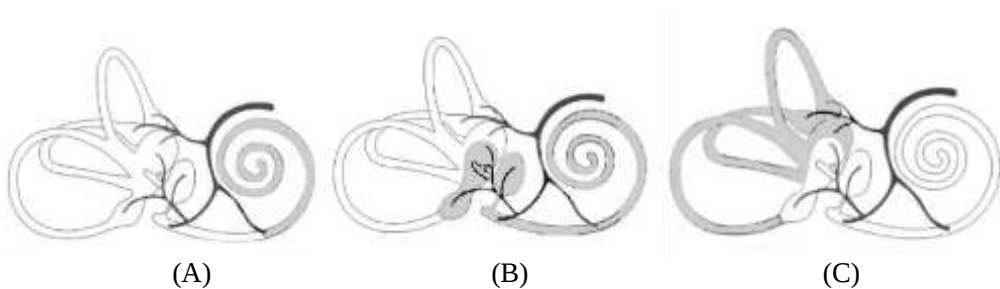


Figure 2. Occlusion of the cochlear (A), vestibular-cochlear (B) and vestibular arteries (C). (From: <http://www.orl.uniroma2.it/ischemia.htm>).

AUTOIMMUNE THEORY

The first report of an autoimmune inner ear disease (AIED), dates back to McCabe (1979) [21]. The autoimmune theory of Sudden Hearing Loss postulates the existence of autoantibodies or activated T-cells that directly target constituents of the inner ear. Antigens occurring on a variety of host molecules, such as type-II collagen, β -actin, cochlin, β -tectorin, cochlear proteins (P30 and P80), cardiolipids, phospholipids, serotonin and gangliosides have been singled out as the putative targets. As of yet, however, the most compelling case concerns a protein called choline transporter-like protein 2 (CTL2).

Finally, the higher frequency of specific HLA alleles in patients that respond well to corticosteroid therapy has been observed, lending further support to the autoimmune theory [22-26]:

- (A): Reduced blood flow to the cochlear artery affects the medium and apical parts of the cochlea, resulting in audiometric deficit limited to medium - and low frequency tones.
- (B): Reduced blood flow at the level of the vestibular-cochlear artery affects the basal part of the cochlea, resulting in audiometric deficit of high-frequency tones associated with vertigo.
- (C): Reduced blood flow in vestibular artery manifests clinically as significant vertigo due to injury of the three semicircular canals.

TREATMENT

As mentioned above, treatment of SHL is a controversial matter and the idiopathic category has been treated by a wide range of approaches. Within the various treatments proposed, glucocorticoids remain the agents most relied on, although via different routes of administration: either oral or intratympanic steroids or their combinations [27, 28]. Nonetheless, Table 2 includes a list of therapeutic modalities which have been adopted, some of which are currently in use for the treatment of SHL.

Table 2. Therapeutic modalities of SHL

Anti-inflammatory/immunologic agents
Steroids
Prostaglandin
Cyclophosphamide
Methotrexate
Diuretics
Hydrochlorothiazide/triamterene
Furosemide
Antiviral agents
Acyclovir
Valacyclovir

Table 2. (Continued)

Vasodilators Carbogen Papaverine Buphenine Naftidrofuryl Thymoxamine Prostacyclin Nicotinic acid Pentoxifylline
Volume expanders/hemodilutors Hydroxyethyl starch Low-molecular-weight dextran
Defibrinogenators Batroxobin
Calcium antagonists Nifedipine
Other agents and procedures Amidotrizoate Acupuncture Iron Vitamins Procaine

PROGNOSIS

Statistical data from case series indicate that 25% of cases evolve with full recovery of hearing, 50% have only partial recovery, while the remaining 25% of patients experience permanent hearing impairment [29-31]. In a study of 270 patients in Sicily, included in one review, the following five prognostic factors were identified:

- a) *Type of Therapy*: combined intratympanic and systemic steroids produced more favorable results;
- b) *Type of Curve*: an upward curve increased the margins for improvement;
- c) *Hypertension*: a hypertensive state reduced the likelihood of recovery;
- d) *Vertigo*: severe vertigo correlated with significantly worse outcomes than no vertigo;
- e) *OAE*: presence of OAEs had positive prognostic significance [32].

CONCLUSION

Sudden sensorineural hearing loss is an issue of primary concern to otolaryngology, given its clinical relevance and potential for disabling outcomes. Arguably, hearing loss negatively impacts quality of life, social and work-related relationships, often representing not only a communication barrier, but also a disconnect from their surroundings for those affected, with the inherent risk of emotional isolation [33]. Despite the advances made, many aspects regarding etiology, pathogenesis, diagnosis and therapy remain elusive and/or controversial. The recent increase in incidence, reported in the literature, probably due to a host of new and widespread pathological noxae, along with the emergence of new therapeutic protocols, render the discussion regarding these issues quite timely. Finally, there is consensus among authors that Sudden Hearing Loss should not go untreated, because many treatments provide at least some margin of benefit and functional recovery, thus improving the patient's quality of life [34-36].

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Chapter 62

CAUSE, PATHOGENESIS, CLINICAL MANIFESTATIONS AND TREATMENT OF MENIERE'S DISEASE AND ENDOLYMPHATIC HYDROPS

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ABSTRACT

Meniere's disease (MD) is characterized by the triad of fluctuating hearing loss, episodic vertigo and tinnitus, and by endolymphatic hydrops found on postmortem examinations. Since the description of endolymphatic hydrops by Hallpike and Cairns all the physiopathology of Meniere's symptoms have been based on assumption that the pathologic lesion was the cause of the symptoms. Paparella came out term and concept towards understanding of a disease was, "pathogenesis," which applies to all otological diseases, in general and in particular within this context of MD, which allows us to better understand this disease. After Schuknecht proposed the theory of membranous rupture causing the mixing up of endo and perilymph leading to the appearance of Meniere's symptoms. Lawrence proved this theory with research on experimental animals. In 1995 the AAO-HNS criteria defines "Possible MD, Probable MD, Definite MD and Certain MD. In 1995 the Committee of Barany Society proposed a classification that is similar to the AAO-HNS criteria, it includes only two categories: definite MD and probable MD. A variety of medical and surgical treatments have been developed to treat or control the symptoms. The treatment can be divided into non-destructive and destructive procedures.

Keywords: Meniere disease, hearing loss, deafness, inner ear, endolymphatic hydrops

INTRODUCTION

Endolymphatic hydrops is the increase of fluids in the inner ear. The morphological substrate of Meniere's disease, becomes histomorphologically evident by excavation of the

Reissner's membrane in the paraffin sections of the cochlea. Although, Paparella described the cause (multifactorial inheritance, genetic) and pathogenesis (endolymphatic absorption) of Meniere's disease and its symptoms (mechanical and chemical); there are diseases that, according to Paparella, can predispose patients to endolymphatic hydrops and Meniere's disease. These diseases include: advanced otosclerosis with otosclerosis obstructing the vestibular aqueduct, chronic inactive otitis media and mastoiditis, syphilis, delayed MD symptoms, endolymphatic hydrops from childhood measles or mumps and sometimes sudden deafness. The latter responded well to medical and surgical therapy. Pathophysiology of symptoms of MD (vertigo, deafness, pressure, tinnitus, loudness intolerance) can be assessed through animal studies; observations of patients clinically and in sequential histopathological studies in patients with MD. Besides hydrops of pars inferior, there are hydrops of the pars superior, as well, with utricle enlargement. This would have allowed for potassium rich endolymph to bathe the basal surface of hair cells as well as the eighth cranial nerve endings. Repeated exposure to toxic potassium levels could cause vertigo episodes and a decline in hearing. There is currently no gold standard treatment for MD and endolymphatic hydrops. Non-destructive methods aim to reduce the symptoms of MD through dietary restrictions as well as through the use of betamethasone, citicoline, cinnarizine and diuretics. Isosorbide, is also used for MD to improve the endolymphatic hydrops. As with the cases of destructive procedures, surgical decompression of the endolymphatic sac, surgical or chemical labyrinthectomy and vestibular nerve section are applied in intractable cases. Recently, in research literature about MD, improvement in vertigo and hearing in patients with MD were described after application of positive pressure to the middle ear using the Meniett device.

CAUSE OF MENIERE'S DISEASE

In the mid- nineteenth century, the classical triad of episodic disabling vertigo (Thomas et al. 2018), fluctuating sensorineural hearing loss (Salvago et al. 2017, Martines, Maira, and Ferrara 2011), tinnitus (Sireci et al. 2012, Salvago et al. 2012, Neri et al. 2009), and a feeling of aural pressure was known as "apoplectic cerebral congestion" and was felt to be a brain disorder. Meniere demonstrated that this phenomenon was due to a labyrinthine dysfunction rather than a brain disease. After Guild discussed the longitudinal flow of endolymph, leading to the knowledge that the endolymphatic sac is the site of the outflow of endolymph in guinea pigs (Guild 1927). Numerous histopathological studies have clearly described, the importance of endolymphatic hydrops and Meniere's disease. Hydrops has been demonstrated to involve both the scala media and the otolithic organs of the inner ear. Hydrops has rarely been associated in only the vestibular portion, but it has been seen to involve only the cochlear portion (Dispenza, Cappello, et al. 2013). Traditionally, Meniere's symptom-complex has divided into two categories: the so-called Meniere's syndrome for which a known cause exists, and Meniere's disease, in which the process appears to be idiopathic (Paparella 1984). Subsequently, Paparella proposed a new simpler classification: a Meniere's disease extrinsic and a Meniere's disease intrinsic. The first is caused by etiological agents that have been shown, through histopathological correlations, to lead to hydrops and the symptomatology of Meniere's disease. These include etiological agents such as syphilis (Pulec 1972), trauma (Paparella and Mancini 1983), otosclerosis (Yoon, Paparella, and Schachern 1990), chronic

otitis media (Martines et al. 2016, Ballacchino et al. 2015), allergy, tumors, leukemia and autoimmune disorders. The second category to consider is the intrinsic factors leading to Meniere's disease. Intrinsic factors are associated with multifactorial inheritance (Paparella 1985), as a cause can include extrinsic contributing factors as well as underlying intrinsic factors such as genetic predispositions and developmental anomalies (Martines et al. 2015, Fung et al. 2002). Of these the most important is genetic. Recently it is been observed the phenotypic and molecular changes in the organ of Corti auditory sensory epithelia and an increase in the number of hair cells and supporting cells, which suggested proliferation of those cells after knockdown of protein Hes 1 (hairy and enhancer of split) and protein COUP-TF1 (COUP Transcription Factor 1) using shRNA (short hairpin RNA) in the organ of Corti organotypic culture of three-day postnatal mice (Tang, Alger, and Pereira 2006). Multiple anomalies were found during endolymphatic sac surgery. These findings were seen in many mastoidectomies for chronic mastoiditis. The findings included hypopneumatization of the mastoid, a sigmoid sinus that is not lateral, but medial and anterior, hypo-development of the aditus and supra pyramidal recess and most importantly Trautmann's triangle, that plate of bone separating the sigmoid sinus from the posterior semi-circular canal which also separates the mastoid from the posterior cranial fossa. Trautmann's triangle may be oriented in a more vertical than horizontal orientation, but most importantly Trautmann's triangle is often reduced in size and can be absent in too many cases. In these patients the sigmoid sinus abuts against the bony wall of the solid angle containing the posterior semi-circular canal. In these cases it can be difficult to gain access to the dura containing the endolymphatic sac beneath the solid angle. Meniere's disease is defined by AAO-HNS as "an idiopathic disease involving the inner ear, that is characterized by vertigo, hearing loss and tinnitus. Meniere's disease has become accepted as the name used to describe these symptoms when they are presumed to be due to hydrops.

PATHOGENESIS OF MENIERE'S SYNDROME

Meniere's syndrome will be described in a number of proposed pathogenic mechanism. These include obstruction of the endolymphatic duct or dysfunction of the endolymphatic sac, overproduction (or up-regulation) of endolymphatic volume, infections, either bacterial or viral, immune-mediated etiologies, genetic causation or predisposition, and vascular disorders.

Endolymphatic hydrops of the membranous labyrinth was described in the pathogenesis of Meniere's syndrome by experiment of Kimura e Schuknecht (Kimura 1982) by surgical obstruction of the endolymphatic duct in the guinea pig. Surgical dissection or cauterization of the sac may cause endolymphatic hydrops in the guinea pig. Histological examination in several human temporal bones showed the presence of peri saccular fibrosis in the endolymphatic duct or sac in patients with Meniere's disease compared to normal (Ikeda and Sando 1984). Hypoplasia of the vestibular aqueduct as a cause of Meniere's syndrome has been suggested by an histological study of the human temporal bone and a difference in the radiographic appearance of the posterior fossa dural plate and the position of the lateral venous sinus. Also, small anatomical size, non-visualization of the duct using RMN and possible obstruction of the vestibular aqueduct by a diverticulum of the jugular bulb, have

been described in some patients with Meniere's syndrome. Common to all of these observations is that the size of the duct or its capacity for radiographic visualization is correlated in some way with the function of the sac and fluid homeostasis of the inner ear. Although obstruction of the endolymphatic duct has been seen in a few human temporal bone specimens with endolymphatic hydrops and concomitant otosclerosis, frank obstruction of the endolymphatic space has been seen in a minority of temporal bones from patients who in life had Meniere's syndrome. The obstruction of some part of the endolymphatic compartment in patients with Meniere's syndrome may be the result, rather than the cause, of endolymphatic hydrops and due to displacement and distortion of limiting membranes of the inner ear (Sando and Ikeda 1984) (Masutani et al. 1991).

As an alternative to defective resorption of the endolymph, it has been suggested that the up-regulation, or overproduction, of endolymph could be another cause for the increased volume of the endolymphatic space found in temporal bones from patients with Meniere's syndrome. Plasma vasopressin levels and plasma antidiuretic hormone (P-ADH) have been demonstrated, by Takumida M. et al, to be elevated in patients with a clinical diagnosis of Meniere's syndrome. Keithley et al. could not demonstrate a significant increase in $\text{Na}^+\text{-K}^+$ ATPase in the stria vascularis from patients with Meniere's syndrome, compared to normal patients (Keithley, Horowitz, and Ruckenstein 1995). In fact, degenerative changes in the lateral cochlear wall in human Meniere's syndrome, would imply decreased activity in at least some enzymatic systems in endolymphatic hydrops. Sterkers et al. have described two osmotic gradients in the cochlea, one between the perilymphatic and endolymphatic spaces, and another within the endolymphatic space from apex to base. They concluded that interference with either gradient may cause endolymphatic hydrops. Juhn et al. have described the possible role of intrinsic metabolites of arachidonic acid in the fluid homeostasis of the inner ear and the interaction of external factors as drugs, stress hormones, and noise, with intrinsic perilymphatic prostaglandin levels and osmolarity.

Both bacterial and viral pathogens have been proposed as etiological agents in Meniere's syndrome. The classical example of bacterial causation of endolymphatic hydrops is syphilis, involving the endolymphatic duct, which includes generalized mononuclear leukocytic inflammatory response and endarteritis, that may also be involved in the pathogenesis of hydrops. In addition endolymphatic hydrops may also be caused by acute or chronic otitis media secondary to passage of bacterial toxins into the inner ear via the round window membrane. A delayed endolymphatic hydrops provides indirect evidence for viral causation of Meniere's syndrome. Endolymphatic hydrops seems to occur months or years following a previous damage to the inner ear, which in some cases may have been viral.

There are a number of known immune-mediated systemic diseases, which also cause inner ear symptoms and endolymphatic hydrops such as Cogan's syndrome and polyarteritis nodosa. In a number of studies evidence of immune hyperactivity has been demonstrated in patients with Meniere's syndrome. Circulating immune complexes have been demonstrated in the serum of some patients with Meniere's syndrome. More recently, a number of articles have demonstrated that 30% of patients with Meniere's syndrome have been reported to have circulating antibodies that reacted with a 58-kilodalton (kDa) antigen generated from animal inner ear protein. Similarly, circulating serum antibodies to a 68-kDa protein were found in some patients with Meniere's syndrome and in some patients with delayed endolymphatic hydrops (Rauch et al. 1995). Hydrops has been demonstrated following a Type 3 allergic reaction, and immunization against Type II collagen. It is clear that a number of disorders

known to be immune-mediated may produce hearing loss and also endolymphatic hydrops (Fattori et al. 1994).

It also suggested that disorders of the microcirculation of the inner ear, including the venous drainage, may be significant in the pathogenesis of Meniere's syndrome. In the classical model of Meniere's syndrome, it has been suggested that endolymphatic hydrops may not be entirely due to physical obstruction of the endolymphatic duct, but may be partially mediated by interference with microcirculation of the endolymphatic sac of the vein at the vestibular aqueduct. It is demonstrated that endolymphatic hydrops in disorders of the microcirculation of the inner ear is immune-mediated in which a significant perivascular inflammatory response is common.

Genetic predisposition to development of endolymphatic hydrops is based on immune-regulatory mechanisms. There is an increased prevalence of the haplotype HLA B8/DR3 in patients with Meniere's syndrome.

Inner ear damage may leads to detachment of the otoliths causing Tumarkin's crisis with drop attack caused by a paroxysmal positional vertigo, which may be treated by maneuvers in the non-active phase (Dispenza, Kulamarva, and De Stefano 2012, Dispenza et al. 2011).

TREATMENT OF MENIERE'S DISEASE AND ENDOLYMPHATIC HYDROPS

The treatment of Meniere's disease remains one of most controversial areas in the field of otolaryngology. The most significant obstacle to define treatment is a lack of understanding of its underlying etiology and a variety of therapeutic options have been studied with conflicting results. Once an attack is established, vestibular suppressant and antiemetic medication have been used to control the vertigo, in association with electrolyte adjustment and rehydration. Treatment can be divided into non-destructive and destructive procedures. Non-destructive methods aim to reduce the symptoms of Meniere disease through dietary restrictions and lifestyle (voluptuary habits, greasy and allergic foods) as well as through the use of diuretics, steroids, drugs modulating the cholinergic system (scopolamine, atropine), or the histaminergic system (dimenhydratate, promethazine), or GABA system (benzodiazepine). On the other hand there are medications acting on voltage-gated ionic channels like the calcium channel blockers (nimodipine, flunarizine, cinnarizine). Betahistine is currently used in European countries for the management of Meniere disease. Recently, experimental and clinical studies on antisecretory system as a clinical innovation in Meniere's disease have been published. As for destructive procedures, surgical decompression of the endolymphatic sac, surgical or chemical labyrinthectomy and vestibular nerve section are applied for intractable cases. Meniett device is used to reduce vertigo and hearing in patients with Meniere disease after application of positive pressure to the middle ear.

A diet low in salt (<2 g) has been the mainstay of therapy. Sodium retention may result from endogenous hormonal responses to stress. No evidence indicates that sodium restriction alters the progression of the hearing loss, but it seems to help control symptoms significantly in many patients. Next, we suggest that patients avoid consuming caffeine, tobacco, alcohol, chocolate and allergens. Those patients who consume these seem to suffer more episodic dizziness and aural pressure.

We routinely use hydrochlorothiazide/triamterene, starting at a low dose (one 25-mg tablet per day for one week, after one 25 mg tablet every other day for two weeks, after one 25 mg tablet twice a week for two weeks) to control metabolic symptoms and reduce the sodium load on the inner ear. With this therapy, there is a need to supplement loss of liquids with potassium. Blood pressure can be measured before treatments and a week after; if it is low to begin with, we may not use diuretic therapy, and it may stop therapy if pressure drops later. It is also described the use of osmotic diuretics (mannitol, glycerol) administered intravenously. The rationale for their use is based on the supposition that these drugs can alter the fluid balance of inner ear, leading to a depletion of endolymph and a correction of hydrops (Stahle 1984).

Oral corticosteroid use is not advisable in patients with classic Meniere disease, but might it be advisable in patients with bilateral Meniere's symptom complex. Treatment with high doses oral of prednisone (1mg/Kg/day for five days and then taper it slowly over a further ten days). If patients' response is significant, we may reinstate the therapy, prolonging the use of the steroid until we reach a stable audiogram and symptomatology. The use of oral or intratympanic (dexamethasone) corticosteroids has also been proposed both to reduce the acuity of the crisis and to promote audio-vestibular recovery (Hargunani et al. 2006, Dispenza, De Stefano, et al. 2013).

In the past many patients used a patch for preventing motion sickness as well as a treatment for chronic low- grade dizziness, but manufacturing problems have made this drug unavailable. A tablet of 0,6 mg of atropine sublingually is an effective method of stopping an attack of vertigo. The atropine is absorbed through the oral mucosa and causes a parasympathomimetic blockade. A subcutaneous injection of atropine 0,4 mg is useful in an emergency room setting to help arrest an active attack.

Histaminergic system drugs are often prescribed for patients with dizziness or vertigo. The anti-emetic action is associated with a sedative effect, which many patients find intrudes on their ability to function during day-to-day. Antihistamines and phenothiazines, strong vestibular suppressants, can be used as anti-emetics in the control of vertigo; patients with Meniere's disease are often plagued with nausea and vomiting, as well as dizziness. Potentially habit- forming drugs must be used with care so as not to create dependency. They must be used only for a few days only because of their side effects (sedation, drowsiness) that delay the spontaneous vestibular compensation and slow down the recovery process. Benzodiazepines act on the cerebellar GABAergic system that inhibits vestibular nuclei response and on glycine receptors of the vestibule-spinal reflex that regulate the postural tone. Among this class, diazepam, clonazepam and lorazepam are used the most (Padoan et al. 1990).

Calcium channel blockers show vestibular suppressant activity because of their anticholinergic and antihistamine properties. They may act on the calcium channel of the vestibular dark cells modifying the ionic concentration in the endolymph. Side effects are tremors, drowsiness, weight gain and depression. Available in this category are flunarizine, cinnarizine, nimodipine and verapamil; these latter have been proposed in treating vertigo of vestibular peripheral origin and Meniere's disease particularly.

All the molecules described, separately or in combination, constitute a possible treatment during a crisis of Meniere's disease. The method of administration depends on the development of vegetative symptoms and the availability in the formulation of each molecule. It could be oral, intramuscularly, intravenously or rectally. It is important to remember that,

because of the action inhibiting the vestibular compensation of most of these drugs, their use should be limited to the acute phase and stopped as soon as possible (Martines et al. 2012).

Betahistine favors vestibular compensation and it may play an important role in helping patients to recover more quickly after each episode. Betahistine, an analogue of histamine with strong inverse agonistic action on the H3 histamine receptors, is currently used in European countries for the management of Meniere's disease. It significantly reduces the incidence and severity of vertigo when compared to cinnarizine, flunarizine or Ginko biloba. Betahistine efficacy can be explained by mechanisms targeting the histamine receptors at three different levels: the vascular tree, the central nervous system, and the peripheral vestibular system. In patients with Meniere's disease, betahistine reduced the intensity and frequency of vertigo significantly. However, the therapeutic effect of betahistine is dose- and duration dependent. High doses of betahistine (at least 48 mg/day) and long-term betahistine treatment (six to nine months) seem two necessary requirements for the prophylactic treatment of Meniere's disease and the improvement of vestibular compensation. According to the new theory of the Meniere attack as an ischemia/reperfusion disorder of inner ear sensory tissue, betahistine could therefore regulate and normalize the reduced perfusion pressure in the inner ear of patients with endolymphatic hydrops (Lacour 2013).

The anti-secretory factor (AF) is a 41 Kd protein secreted in plasma and other tissue fluids in mammals. This protein provides protection against diarrheal diseases and intestinal inflammation. It has been postulated that AF may act as a modulator of water and ions by regulating chloride homeostasis through membranes, and an interaction with aquaporins has been claimed. The endogenous plasma level of anti-secretory factor is increased by enterotoxins and surprisingly also by certain food constituents. Specially Processed Cereals (SPC) is an AF-inducing medical food, developed by the Swedish R&D company, as well as an AF-rich egg yolk powder, Salovum. SPC-Flakes® are especially processed cereal optimized to increase endogenous AF plasma levels. A 14-28 days-long period of intake of SPC-Flakes® is necessary to obtain a significant AF plasma concentration, commonly followed by a positive clinical outcome. Because of the effects on hypersecretion in the gastro-intestinal tract, it was hypothesized that anti-secretory treatment with SPC could be valuable in other instances where fluid imbalance is thought to play a role, such as Meniere's disease. In an open pilot study, in some patients, the attacks of rotatory vertigo were reduced and hearing was normalized. Studies in rats using immunohistochemistry methods demonstrated that AF was localized to the cochlea and the vestibule of the inner ear, which led the authors to propose that AF could be a new regulator of endolymph. Recently, various authors have reported a significant reduction of vertigo in patients with Meniere's disease treated with SPC-Flakes® ranging between 50% and 60%. Significantly other authors have correlated the reduction of episodes of vertigo with an increase of AF plasma levels in patients with Meniere's disease performing the therapy. Today, the antiseecretory factor protein is recognized as a fundamental regulator of fluid balance in mammals (Leong, Narayan, and Lesser 2013).

When intractable incapacitating vertigo cannot be controlled by other means, surgical intervention must be considered. In this situation it is desirable to recommend a procedure that offers a high likelihood of vertigo control with maximum hearing preservation.

We can divide intractable vertigo into conservative (endolymphatic sac surgeries, saculotomy, criotherapy, fistulization of the labyrinth) and destructive (vestibular neurectomies and labyrinthectomies). The first type, conservative surgery for Meniere's disease had been

used relatively infrequently, and reports by otologists were often not enthusiastic about the procedure's value.

Paparella published very good results of a technique with decompression and drainage. He emphasized that the experimental demonstration of the endolymphatic sac's role has not been conclusive, however, it appears that the sac does have a significant function in endolymphatic homeostasis. When endolymphatic homeostasis is disturbed and hydrops occurs, the sac appears a conceptually excellent site for decompression of the endolymphatic space. The sac is relatively distant from the cochlear and vestibular organs. There is also some evidence that the direction of the flow within the endolymphatic duct is away from these organs toward the sac. The surgical technique is essentially the same as any other transmastoid endolymphatic sac procedure, with the exposure of the endolymphatic sac below the lateral sinus. It is important to try to expose as much of the endolymphatic sac as possible. A probe is used to locate the endolymphatic duct to measure the amount of endolymphatic sac hidden by the posterior semicircular canal. The lateral edge of the endolymphatic sac is gently excised and lifted off the underlying dura. A probe can be placed between the endolymphatic sac and the dura. Next, the endolymphatic sac is transected inferiorly using a small knife. The endolymphatic sac can then be lifted off the dura and dissected superiorly, so the only attachment remains at the duct. The duct is then grasped with angled cupped forceps and avulsed to try to remove as much of the intraosseous portion as possible.

Chemical labyrinthectomy consists of instilling into the middle ear streptomycin or gentamicin with the intention to reduce or abolish vestibular activity in the afflicted ear whilst preserving hearing. Gentamicin is less cochleotoxic than streptomycin when instilled directly into the middle ear. The absorption of drugs into the inner ear is via the round window or the annular ligament of the oval window. The treatment protocols using intratympanic gentamicin can be divided into fixed dose protocols and titration protocols. Fixed dose protocols aim to administer a fixed dose of gentamicin over a predetermined interval. The treatment is discontinued earlier only if the patient develops symptoms or signs of ototoxicity. Titration protocols aim to administer gentamicin until the patient demonstrates evidence of ototoxicity. Our protocol consists of instilling gentamicin 40 mg/cc through a single weekly injection technique. The solution is introduced into the middle ear with an epidural needle into the anterior-inferior quadrant of the eardrum until the middle ear is full. A bone conduction audiogram and clinical assessment is performed daily before the next administration. Low dose, varying interval, protocols offer the attraction of a reduced incidence of hearing loss (De Stefano et al. 2007). However, they require a significant time investment and may require multiple treatments for the control of vertigo. Intratympanic gentamicin is an effective treatment modality for the control of vertigo in severe unilateral Meniere's disease. It offers an alternative to the traditional surgical procedures of vestibular neurectomy and labyrinthectomy. Complete or substantial control of vertigo is noted in 90% of patients. Vestibular neurectomy is considered when medical management fails. In the retrolabyrinthine approach to the vestibular nerve combined with the retrolabyrinthine-retrosigmoid approach to the vestibular nerve, the facial nerve is routinely monitored. In the retrolabyrinthine approach an anteriorly based postauricular flap is elevated with the periosteum and postauricular muscles in a single layer. A mastoidectomy is performed and bone is removed over and behind the sigmoid sinus. The endolymphatic sac and the surrounding dura are widely exposed. The vertical portion of the facial nerve, the posterior wall of the external auditory canal, and the posterior semicircular canal are identified and preserved. The sigmoid

sinus is collapsed and retracted posteriorly using a retractor. The dura anterior to the sigmoid sinus is incised, creating an anteriorly based flap around the endolymphatic sac. A 1,5-2 cm wide Penrose drain is placed over the cerebellum, which is gently retracted as the arachnoid is opened with an arachnoid dissector instrument to allow the cerebrospinal fluid to escape. The vestibular nerve section is then performed under high-power magnification. The dura is closed using interrupted 4-0 silk sutures. Temporalis fascia is placed over the dura, the mastoid cavity is then filled with adipose tissue and the wound closed in layers. However a watertight closure is generally not possible and the 10% incidence of cerebrospinal fluid leakage has led to an evolution in technique of the retrosigmoid-internal auditory canal approach (RSG-IAC) and finally of the combined retrolabyrinthine-retrosigmoid approach (RRVN).

The RSG-IAC approach was developed in an attempt to improve results of the vestibular neurectomy near the labyrinth, where the fibers are more clearly delineated and decrease the incidence of cerebrospinal fluid leakage. Within the internal auditory canal, the cleavage plane between the cochlear and vestibular fibers is more developed near the labyrinth and thus a more complete and selective vestibular nerve section can be performed. A posterior fossa craniotomy is performed behind the sigmoid sinus. After the cerebrospinal fluid is released from the cerebellopontine cistern the cerebellum falls away. The jugular dural fold and the VIIIth cranial nerve are identified. The posterior wall of the external auditory canal is drilled with a diamond burr to the singular canal. Next, the dura in the internal auditory canal is incised. The superior vestibular nerve and the singular nerve, the branch of the inferior vestibular nerve to the posterior semicircular superior canal (SSC), are sectioned at this point. The branch of the inferior vestibular nerve to the saccule is preserved since the saccule has no known vestibular function in man and sectioning it would place the hearing at risk. With this procedure, no abdominal fat is needed to fill the defect since this approach does not require a mastoidectomy. Also, the dura can be closed in a watertight fashion. The retrosigmoid approach solved the cerebrospinal fluid leakage problem, however, because of the frequent incidence of severe headaches, this approach was discontinued in 1987. The headaches were felt to be related drilling the bone over the internal auditory canal, causing a bone dust arachnoiditis.

The combined RRVN approach represents a further evolution in posterior fossa approaches to vestibular neurectomy. A limited mastoidectomy is performed, opening a few mastoid air cells. The bone over the sigmoid sinus is removed from the transverse sinus to the jugular bulb of about 3 cm. The dura posterior to the sigmoid sinus is exposed for 1,5-2 cm. A dural incision is made 3 mm behind and parallel to the sigmoid sinus. The sigmoid is retracted forward using three stay sutures placed along the dural cuff. This affords visualization of the posterior wall of the temporal bone, the jugular dural fold, and allows wide exposure of the cerebellopontine angle without retraction of the cerebellum. After the cerebellopontine angle cistern is opened and cerebrospinal fluid released, the vestibular nerve is identified and sectioned. On occasion when a cleavage plane cannot be visualized, the internal auditory canal can be opened and the nerve sectioned, as outlined under the RSG-IAC approach. The internal auditory canal is no longer opened for vestibular nerve section. In cases with a poor cleavage plane, the superior half of the VIIIth nerve is sectioned near the brain stem. Once the procedure is completed, the exposed mastoid air cells are sealed with bone wax and the dura is closed in a watertight fashion with interrupted silk sutures. Abdominal fat is used to fill in the bony defect for cosmetic purposes and to reinforce the

dural closure. The skin is closed with staples without a drain. This approach was developed in an effort to streamline the procedure further by shortening the operating time, making a watertight closure of the dura possible, and allowing exposure for drilling the internal auditory canal when necessary.

Pressure treatment is regarded as one of the therapeutical options to offer to disable Meniere's disease, when the patients are not responding to any medical treatment. The Meniett device is a portable instrument that allows a patient to self-administer treatments at home, whenever required. The Meniett device has become, at some centers, a conservative procedure without risk of additional damage to the inner ear, such as when applying intratympanic gentamicin. This therapy started to be always proposed to those Meniere's patients already selected for vestibular neurectomy surgery. The protocol consisted in insertion of a short-term trans-tympanic ventilation tube and in one-month treatment that started the same day. Each patient was instructed to use the device five times per day, for three minutes per session. During the month of treatment, each patient was asked to fill in a diary, noting any symptom related to Meniere's disease (Gates et al. 2006).

A simple surgical intervention is performed, under local anesthesia, inserting a short-term trans-tympanic ventilation tube, with the aim of reducing intralabyrinthine pressure and decreasing the potential high pressure of the middle ear. Some patients report an improvement or a disappearance of vertigo (Park, Chen, and Westhofen 2009, Dispenza et al. 2015).

CONCLUSION

Meniere's disease raises great interest for many reasons:

- It is necessary to make a precise clinical analysis to decide the diagnosis;
- Specific examinations are available to confirm the diagnosis;
- The therapeutic medical or surgical support is various and variable;
- Clinical and research pathways are multiple.

Beyond the clinical expressions, Meniere's disease imposes a better understanding of mechanisms involving homeostasis of the inner ear and its troubles. The diversity of clinical expression, in particular the variability of the intensity and symptoms, justifies individual care to establish appropriate treatment.

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Chapter 63

AUTOIMMUNE INNER EAR DISEASE

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ABSTRACT

Nowadays, autoimmune deafness does not appear to be as a well-defined nosological entity, although the ability of the inner ear to react to genetic, environmental and autoimmune phenomena has been demonstrated. The scientific evidence shows sensorineural deafness, usually bilateral, rapidly progressive and debilitating, which mostly affects women (from 30 to 50 years) and is associated with vestibular symptoms and 30% of autoimmune diseases. The clinical diagnosis, without specific laboratory tests, is made most of the time, as exclusion.

Generally, autoimmune deafness is rapidly progressive and is characterized by a reduction of more than 30 db on three adjacent frequencies. It appears over a period of weeks or a few months. The best diagnostic test, in general, is the improvement of hearing observed after treatment with corticosteroids or immunosuppressants.

Regarding the onset of autoimmune deafness, it is possible to identify different factors: genetic hypothesis with particular HLA suggesting genetic susceptibility to pathology and environmental hypotheses, namely exogenous (viral, toxic) factors that ease its onset. Otoscopy is usually within limits, audiometry doesn't show particular features and it is possible to observe curves with falling plateaus on acute sounds. The differential diagnosis is important with diseases such as carcinosis, ear tumors, ototoxicity, syphilis, and Ménière's disease. In absence of specific tests, what is typically provided is: a) dosage of inflammation markers (ESR and PCR); b) search for antibodies that can be found in autoimmune diseases (ANCA, ANA Cryoglobulins, Anti-endomysial

antibodies, Anti-core, Anti-Mitochondria, Anti-muscle smooth, etc.); c) viral serology; d) tests to explore humoral and cellular immunity.

Therefore, therapy involves not only the use of corticosteroids (oral or transtympanic) or immunosuppressants, but also of plasmapheresis, gamma globulin and, finally, the installation of a cochlear implant.

Keywords: autoimmune, hearing loss, deafness, immunology, ear

INTRODUCTION

Already in 1958, Lehnhardt studied recursive bilateral cases of deafness, attributing them to the presence of autoantibodies. The immune system is complex and formed by a series of balances that allow to recognize our body the self from non-self. If one of these mechanisms that guarantee equilibrium should fail, an autoimmune pathology occurs.

The Autoimmune Inner Ear Disease (AIED) was first described by McCabe in 1979 as Bilateral Sensorineural Hearing Loss (SNHL) that progressed over weeks to months and was responsive to immunosuppressive agents; hence he proposed an autoimmune mechanism. Since that time, a large body of evidence in support of the immune hypothesis has been proposed; however, the underlying pathophysiology remains unknown and is likely to be varied. Elucidating the underlying immune mechanism is important, because immune-mediated hearing loss is one of the few causes of SNHL that is reversible.

Inner ear, also called labyrinth of the ear, is a part of the ear that contains organs of the senses of hearing and equilibrium. The bony labyrinth, a cavity in the temporal bone, is divided into three sections: the vestibule, the semicircular canals, and the cochlea. (Dispenza, Cappello, et al. 2013). Within the bony labyrinth is a membranous labyrinth, which is also divided into three parts: the semicircular ducts; two saclike structures, the saccule and utricle, located in the vestibule; and the cochlear duct, which is the only part of the inner ear involved in hearing. The cochlear duct forms a shelf across the cochlea dividing it into two sections, the scala vestibuli and the scala tympani. The bony labyrinth contains the otic capsule, which is denser than the surrounding temporal bone. The entire inner ear is bathed in a cushioning fluid, called the endolymph when it lies within the membranous labyrinth and the perilymph when it separates the bony and membranous labyrinths (Martines et al. 2015, Rizzo et al. 2016, Salvago et al. 2017).

AUTOIMMUNE INNER EAR DISEASE PATHOLOGY

It is complex to have a precise definition of the pathology known as autoimmune deafness, since most of the time the diagnosis is made by exclusion or given by the response to the treatment with corticosteroids.

According to the literature data, autoimmune deafness refers to a rapidly progressive bilateral and asymmetric sensorineural deafness, with associated vestibular signs and a slight prevalence for women in their middle age (factor in common with all the other autoimmune

diseases) and with a systemic disease associated with a percentage that is around 25% of cases.

AIED manifests clinically as SNHL that progress over weeks. Most commonly affects women between the ages of 20 and 50 years. The inner ear is not an immune-privileged site, and the endolymphatic sac is critical for the immune response.

Sudden autoimmune deafness seems to be very rare, and the self-priming residing in the presence of autoimmune agents would destroy or directly affect the inner ear.

Causes of the pathology can be: environmental factors and genetic factors.

Environmental Factors

These are infectious agents (for example, parts of viruses or other infectious agents) that, according to a mechanism of molecular mimicry, would be recognized as non-self structures of the human organism.

Genetic Factors

In the years 2001-2005, 88 patients were recruited and subjected to routine serological tests and also tests for the determination of antibodies hsp70. Patients were divided into three groups: patients with Autoimmune Sensorineural Hearing Loss (ASNHL), patients with idiopathic ASNHL associated with Cogan Syndrome and patients with ASNHL associated with Systemic Autoimmune Disease (SAD). The study confirmed the value of the anti-hsp70 test in the diagnosis of autoimmune deafness, promoting it as a marker capable of identifying an autoimmune origin of hearing loss (Boulassel et al. 2001, Bovo, Aimoni, and Martini 2006).

MicroRNAs (miRNAs) regulate the differentiation and development of inner ear cells. Mutations in miRNAs lead to deafness in humans and mice. Among inner ear pathologies, inflammation may lead to structural and neuronal defects and eventually to hearing loss and vestibular dysfunction. While the genetic factors of these pathways have not been defined, autoimmunity participates in these processes. It is reported that inflammatory stimuli in the inner ear induce activation of the innate immune system via miR-224 and pentraxin 3 (Ptx3). miR-224 is a transcriptional target of nuclear factor κ B, a key mediator of innate immunity. Ptx3 is a regulator of the immune response. It is released in response to inflammation and regulated by nuclear factor κ B. It is shown that miR-224 and Ptx3 are expressed in the inner ear and it is demonstrated that miR-224 targets Ptx3. As a model for the innate immune response, lipopolysaccharide is injected into the scala tympani of mouse inner ears. This resulted in changes in the levels of miR-224 and Ptx3, in addition to activation of the complement system, as measured by immune cell infiltration and activated C3. This suggests that while miR-224 regulates Ptx3 under normal conditions, upon inflammation, both are recruited to offer a front line of defense in acting as responders to inflammation in the inner ear. miR-224 diminishes the innate immune response by downregulating Ptx3 expression, while Ptx3 stimulates the innate immune response (Rudnicki et al. 2014).

Yet a role for development is suggested by intriguing overlaps in particular organs targeted in autoimmune diseases, in this case type 1 diabetes and Primary Sjogren's Syndrome (PSS). Patients with diabetes type 1 have high rates of concomitant PSS, and both conditions are associated with hearing loss and tongue abnormalities. All of these co-occurrences are found in organs tracing their lineage to the developmental transcription factor Hox11, which is expressed in embryonic cells destined for the pancreas, salivary glands, tongue, cranial nerves and cochlea (Lonyai et al. 2008).

Diagnosis

Making a diagnosis of ASNHL is not simple; it is necessary to have an accurate knowledge of the patient in terms of medical history, collection of instrumental examinations, laboratory tests and radiological examinations useful to diagnose any underlying multi-organ pathology.

An interesting retrospective study in which 19 cases of patients with bilateral ASNHL were presented, with clinical features, laboratory tests, instrumental examinations, audiometric and radiological examinations with relative prognosis for each case described. Among these 19 cases, 78.9% of patients presented non-otological diseases with multisystem and multi-organ disorders, with diseases of the central nervous system such as viral or bacterial meningitis, 5 patients on the other hand had pathologies of the concomitant immune system, with characteristic deafness progressive and simultaneous bilateral autoimmune type. It is therefore necessary, first of all, to identify the etiology of the underlying disease by admitting its treatment to treat and try to resolve the associated deafness (Gao et al. 2015).

Currently, there is any reliable test in order to detect immunocompetent cells or direct and specific circulating antibodies against certain labyrinth structures.

The sensitivity and the specificity of the various tests proposed in the literature must be interpreted with caution, since in the absence of standard comparators, there are numerous methodological distortions that can lead astray and therefore towards incorrectly correct diagnoses.

The implementation of the complementary budget, particularly the laboratory one, is a function of the anamnesis where previous personal and family history, traumas of long standing, recent viral syndrome, recent vaccination or intake of an ototoxic drug, must be sought. The otoscopic and vestibular examination with subjective audiometry (audiometry) and objective measures (auditory evoked potentials, otoemissions) and instrumental vestibular tests, will then be completed (Hervier et al. 2010, Dispenza and De Stefano 2012).

Cogan's Syndrome

Cogan's syndrome (CS) is a rare chronic autoimmune disease, characterized by interstitial keratitis and sensorineural hearing loss. It may also be accompanied by systemic vasculitis (large vessel vasculitis, aortitis, medium-sized vessel vasculitis) (St Clair and McCallum 1999). The etiology of CS is still unknown; environmental exposure to toxic substances or pollutants, viral infections, cigarette smoking might be some triggers for the disease (Gluth et al. 2006). The pathogenesis is now supposed to be based on circulating

autoantibodies and endothelial antigens that are found in the inner ear in CS patients, but are not found in the sera of patients with other autoimmune diseases. Lunardi et al. identified “the Cogan peptide” as an amino acid sequence related to six autoantigens; CD148 (a transmembrane protein expressed in the inner ear) and connexine 26 (a gap junction protein highly expressed in the inner ear) are two of these six autoantigens that have been studied. They might be two inner ear targets for autoantibodies (Lunardi, Bason, and Leandri 2002).

Crohn's disease, ulcerative colitis, sarcoidosis, hypothyroidism, and interstitial nephritis and other autoimmune diseases may present in association with CS. That supports the hypothesis that CS is an autoimmune disease too (Grasland et al. 2004).

Usually, CS initially presents with vestibule-auditory pathologies. The most common presenting symptom is sudden bilateral sensory hearing loss. Inner ear manifestations of CS are Ménière's-like attacks consisting of vertigo, hearing loss, tinnitus, ataxia, nausea, and vomiting. Vestibular and auditory dysfunctions develop quickly, and recurrent episodes of inner ear disease result frequently in deafness. Once the hearing loss is deep, vertigo and other vestibular symptoms usually disappear.

According to Oshrat et al. mandatory criteria for CS diagnosis are: sensorineural hearing loss, inflammatory ocular disease (classically interstitial keratitis), alternative causes of inflammation or infection ruled out.

Prevalent additional criteria are vertigo and tinnitus, ataxia and dizziness, fever, weight loss, fatigue, lymphadenopathy, and headache. Possible additional criteria are vasculitis and elevation of systemic inflammatory markers.

There are basically three therapeutic approaches. Topical steroid to treat mild ocular disease without other symptoms. Prednisone (1 mg/kg/day) is prescribed when inner ear, ocular and systemic symptoms are present; this treatment should produce a short period of intense immunosuppression. If improvement occurs doses can be tapered down after 2 to 4 weeks. In cases of relapse, corticosteroid dose should be increased again.¹ Therapeutic doses are chosen according to clinical response, in order to reduce the steroid dosage below 10 mg/day. Additional immunosuppressive drugs are methotrexate, azathioprine, cyclophosphamide, cyclosporine (D'Aguanno et al. 2018).

A biologic therapy using infliximab (anti-TNF- α) could be considered after treatment with steroids if:

- 1) Lack of response to steroids within 2–3 weeks;
- 2) Inability to reduce the steroid dosage below 10 mg/day;
- 3) The use of steroids is contraindicated in light of the patient's medical status (e.g., diabetes, hypertension, or if there are significant side effects).

The use of infliximab as first-line therapy could be started in selected patients:

- 1) Patients with severe ocular involvement, which jeopardizes the patient's eyesight (scarring and elevated intraocular pressure);
- 2) Rapid hearing loss (hearing level approaching 50 Hz);
- 3) When both ears are simultaneously affected;
- 4) Evidence of systemic involvement: large vessels vasculitis, involvement of the heart, kidneys, and nervous system;

- 5) The patient's general condition precludes the use of high-dose steroids (severe heart failure, uncontrolled diabetes, or hypertension).

Vogt-Koyanagi-Harada Syndrome

Vogt-Koyanagi-Harada (VKH) syndrome is an idiopathic, multisystem autoimmune disorder characterized by bilateral granulomatous uveitis with neurologic, auditory or dermatologic symptoms.

Otologic complaints are sensorineural hearing loss, tinnitus and/or vertigo that typically coincide with the onset of ocular pathology (Ondrey et al. 2006).

The diagnosis of VKH disease is based on both ocular and extraocular symptoms and signs. The current diagnostic criteria only include tinnitus, not hearing loss, as an auditory finding (Read et al. 2001).

Nevertheless, according to Morita et al., 89.4% of the subjects affected by VKH included in their study were found to be suffering from hearing loss on the basis of audiometric findings, while only 34.1% complained of tinnitus. This might be explained by the mild degree of hearing loss that can be noticed easily with audiometry but doesn't match with subjective hearing loss. That's why they suggest to do auditory examinations to every VKH patient, in order to evaluate any degree of hearing loss, whether or not the loss is clinically relevant (Morita et al. 2014).

The diagnosis is clinical; the eye exam is fundamental, looking for iridocyclitis and posterior uveitis.

The cochleo-vestibular involvement appears in 33 to 75% of cases. Evolution in deafness is usually progressive; rarely it can be sudden. The severity of this impairment is variable. The prognosis is improved by early diagnosis and treatment, and adequate management based on prolonged corticosteroid therapy with or without immunosuppressors.

Susac's Syndrome

Susac's syndrome (SS) classically presents with the clinical triad of sensorineural hearing loss, retinal artery occlusion and encephalopathy plus the neuroimaging triad of white matter lesions, deep gray matter lesions, and leptomeningeal disease. It's a rare disease. Initial SS is characterised by incomplete clinical or neuroimaging triads; this makes it difficult to be diagnosed.

It is now thought that it is an immune-mediated endotheliopathy that affects the microvasculature of the brain, retina, and inner ear. The incidence of SS is higher in females than in males (3:1), in fact there is a female predominance in autoimmunity diseases. Antiendothelial cell antibodies (AECAs) mediate the endothelial cell injury with consequent deposition of thrombotic material in the lumen of the small vessel (Magro et al. 2011).

Patients with SS must be treated quickly and aggressively. Medical treatments start with a pulse of highly dosed methylprednisolone (1000 mg/day for 5 days), tapering it in the following weeks, according to the patient condition. It is usually provided also an antithrombotic and anticoagulation treatment (García-Carrasco et al. 2011).

In the worst cases, addition of mycophenolate mofetil or rituximab is required, followed by cyclophosphamide when disease is refractory to other medications.

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disorder that can affect joints. In some people, the condition also can damage a wide variety of body systems, including the skin, eyes, lungs, ear, heart and blood vessels. The initial site of disease is the synovial membrane, where swelling and congestion lead to infiltration by immune cells. Three phases of progression of RA are an initiation phase (due to non-specific inflammation), an amplification phase (due to T cell activation), and chronic inflammatory phase, with tissue injury resulting from the cytokines, IL-1, TNF-alpha and IL-6. Patients with RA had a high prevalence of sensorineural hearing loss for high and very high frequencies.

RA is thought to induce conductive hearing loss and/or sensorineural hearing loss. Ahmadzadeh et al. evaluated the function of the middle ear and cochlea, and the related factors in patients with RA; they detected higher bone conduction thresholds in some frequencies of RA patients, but not clinically significant. Otherwise they confirmed that sensorineural hearing loss is significantly more prevalent in refractory rheumatoid arthritis patients. This study revealed that sensorineural hearing loss is frequently due to medical treatment with azathioprine, cyclosporine and etanercept (Ahmadzadeh et al. 2017).

Primary Sjögren Syndrome

Primary Sjögren Syndrome (pSS) is a chronic autoimmune disease characterized by lymphocyte infiltration of both the salivary and lacrimal glands; its main symptoms are dry eyes and a dry mouth. Otologic symptoms may be an early indicator of pSS, but they are also a less-common feature of other autoimmune disorders (Tucci, Quatraro, and Silvestris 2005). Ziavra et al. founded SNHL in 22.5% (9/40) of pSS patients (Ziavra et al. 2000).

The most common hearing impairment has cochlear origin; it often involves high frequencies. Autoantibodies of both cardiolipin and M3 muscarinic receptors in the sera are suspected to play a pathogenetic role in the progressive hearing loss of pSS patients (Tucci, Quatraro, and Silvestris 2005).

The mechanism that leads to sensorineural damage might be vasculitis, neuritis, or an ototoxic effect of the drugs used to treat pSS (Tumati, Casoli, and Parmeggiani 1997).

Polyarteritis Nodosa

Polyarteritis nodosa (PAN), also known as panarteritis nodosa, periarteritis nodosa, Kussmaul disease, or Kussmaul-Maier disease, is a systemic necrotizing inflammation of blood vessels (vasculitis) affecting small- or medium-sized muscular arteries, that typically involves the arteries of the kidneys, of lungs and other internal organs.

According to Wolf et al. the hearing loss that occurs in PAN is due largely to middle ear effusion but usually appears as a mixed type. Pure perceptive hearing loss is rare. A profound,

rapidly deteriorating perceptive hearing loss could be the onset and only one symptom of PAN (Wolf et al. 1987).

Gussen detected that the cochlea as well as the vestibular system exhibited ischemic necrosis of the soft tissue structures with extensive fibrosis and bone formation; that is supposed to be one of the pathogenic mechanism of hearing impairment (Gussen 1977).

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with multiorgan involvement and an incidence of 12.5–39.0 per 100,000 people in the general population (Di Stadio and Ralli 2017). The pathophysiology of SLE is based on the production of autoantibodies that react with self-nuclear and cytoplasmic antigens, creating an immunologic attack on body organs, resulting in tissue inflammation and multiorgan damage (McCarty et al. 1995).

Di Stadio et al. performed a systematic literature review about hearing loss in patients affected by SLE. They assessed that SLE can damage tissues and organs through three different mechanisms: antibody/antigen direct reactions, cytotoxic action, and immune complex deposition (Di Stadio and Ralli 2017).

These mechanisms together create hearing impairment: immune complex deposition plays a central role in the development of inner ear vasculitis and is associated with atrophy of the stria vascularis. Progressive reduction of the vessel caliber increases the resistance in the circulatory system, eventually increasing the blood pressure. Oxygen deficit damages inner ear cells.

According to Di Stadio et al., corticosteroids should be considered as the first treatment option to restore hearing in patients with sudden hearing loss and prevent worsening of progressive hearing loss. If steroid therapy is unsuccessful cyclophosphamide should be used. Monoclonal antibodies should be used in patients with proven resistance to other treatments. Plasmapheresis and anticoagulant treatments could be a good preventive therapy for sudden sensorineural hearing loss (Di Stadio and Ralli 2017).

SPECIFIC TESTS OF THE INNER EAR

The Specific tests of the inner ear can be classified as follow: lymphoblastic transformation test concerning cellular immunity (TTL), western blot (humoral immunity) and indirect immunofluorescence test.

Lymphoblastic Transformation Test Concerning Cellular Immunity

The test consists in incubating the lymphocytes of patients stimulated with antigens belonging to the inner ear (human). To collect the material needed to perform the test, the antigens must be extracted by surgery conducted by translabyrinthine route. During these experiments conducted on a small number of patients, given the complexity of finding the

biological material to perform the study, an increase in gamma interferon by T cells placed in the presence of antigens coming from the inner ear, was noted (Lorenz, Solares, and Williams 2002).

Western Blot

The test aims to identify specific circulating autoantibodies with respect to different antigens present in the human labyrinth, following their migration on a support according to their size and weight.

On this basis several candidate antigens were studied as targets in autoimmune deafness (Suslu, Yilmaz, and Gursel 2009):

- Type II collagen;
- Po-myelin;
- Beta-actin;
- Beta-tubulin;
- Different proteins with a molecular weight of 30, 32, 33, 34, 35, 58, 68, 220 Kda

Also some autoantibodies directed against non-specific inner ear proteins were initially attentions, such as the antibodies directed against the 68 proteins found in western blot up to 60% of cases of isolated developmental sensorineural hearing loss, but also in extra pathologies labyrinthine.

This protein was subsequently identified in the heat shock protein 70, an intracellular protein released in the event of thermal stress. For other authors it would be the CTL2 protein, fundamental in the role of degeneration of the Corti's cells. However, the distribution of CTL2 would not only be limited to Corti's cells, but its molecular similarity to cyclic, suspects an important function also in the transport of molecules from the intracellular environment to the extra cellular environment of the inner ear. This specific protein of the inner ear, however, seems an interesting track even if, to date, a diagnostic test has not yet been developed to actively and easily tests this protein in the diagnosis of autoimmune deafness.

Indirect Immunofluorescence Test

The principle is based on the visualization, starting from human or animal temporal bone sections, of human antibodies that are fixed and taken first from the patient's serum, which confirms that the serum contains specific proteins of the inner ear or non-specific (Yeom et al. 2003).

However, it is possible to simply evaluate that laboratory tests have neither the sensitivity nor the specificity sufficient to confirm that this is an autoimmune deafness and are nevertheless very expensive.

OTHER USEFUL TESTS FOR DIAGNOSIS

An examination of the fundus oculi is essential to understand the presence of the signs of raisins or episcleritis, always in the context of the systemic autoimmune disease.

A Magnetic Resonance Imaging (MRI) of the posterior cranial fossa and the inner ear would be useful in order to found a retrocochlear pathology in the case of asymmetric sensorineural deafness (Piccirillo et al. 2011, De Stefano, Kulamarva, and Dispenza 2012). A CT of petrous bone also plays an important role in the diagnosis in order to found morphological abnormalities of the labyrinth in children (Dispenza et al. 2015).

The diagnosis is based on history, on physical examination, on laboratory and instrumental tests that lead to a general and global classification (Hervier et al. 2010, De Stefano et al. 2011, Dispenza, Gargano, et al. 2011).

THERAPY

Therapies can be classified as follows: corticosteroids, immunosuppressive, plasmapheresis, gammaglobuline, intratympanic injections, cochlear implants, and new frontiers of research.

Corticosteroids

Validated treatment that demonstrates efficacy in autoimmune deafness. This treatment turns out to be the first therapeutic choice even before the diagnostic phase; in fact it is done before having carried out all the investigations of the case. The recommended dose for adults is 1-2 mg/kg per day of methylprednisone for 4 weeks.

The oral delivery route is recommended due intravenous cortisone boluses are considered off-label with regard to the occurrence of sudden or autoimmune deafness. More the treatment is quickly, the greater the degree of improvement of the symptoms obtained.

The actual duration of steroid treatment seems rather uncertain. Periods of continuation of corticosteroid therapy are recommended for 1-2 months, depending on the response (Harris and Ryan 1984). If there is not response within 4 weeks, then the steroid therapy is recommended to interrupt over a period of seven days in descending order, again to avoid altering the hypothalamic-pituitary axis.

In patients who respond, the hypothesis of continuing with 20-30 mg/day for several weeks can be evaluated. In children up to 14 years of age, must be taken into account all the adverse effects that could occur with the introduction of corticosteroid therapy during growth and evaluate any risks and benefits.

Immunosuppressive

Immunosuppressants drugs may be an alternative treatment to the use of corticosteroids. It can be evaluated:

- in those patients who cannot assume steroid therapy;
- in those patients in whom, side effects due to excessive use of strictures, such as myelosuppression or hemorrhagic cystitis, have already occurred;
- in those patients in whom, having obtained a good result with corticosteroids, they want to maintain and strengthen the therapy and the success of the therapy through the use of this class of drugs.

Specifically, the drugs used are methotrexate and cyclophosphamide. Methotrexate is prescribed at a dose of 7.5 mg/week as a single dose, given in combination with folio acid 1 mg/day to minimize the risk of stomatitis.

It is important to monitor the side effects of methotrexate, which include anemia, thrombocytopenia, hepatotoxicity and lung problems.

The side effects of cyclophosphamide instead include bone marrow suppression, infertility, hemorrhagic cystitis, increased risk of prostate cancer and lymphoma. Another drug that is used as an immunosuppressant is colchycin, an alkaloid that prevents microtubule polymerization by blocking them in metaphase, used in anti-inflammatory gout therapy. In animals, its validity in the modification of fluids within the labyrinth seems to be related. The recommended dose is 1 mg/day, although at the moment none of these drugs was approved by the *Food and Drug Administration* (FDA) for the treatment of autoimmune sensorineural deafness.

Plasmapheresis

The blood is purified from all the immunoglobulins with a mechanism very similar to that of dialysis. This therapy is invasive, expensive and unapproved in the treatment of sudden autoimmune deafness.

Gammaglobuline

The intravenous route of administration appears to lead to results similar to plasmapheresis, with greater ease of delivery and fewer side effects. The immunoglobulins would seem to interact with a series of complement factors, such as cytokines, mediators of immunity and cellular fractions, in order to attenuate the autoimmune response in autoimmune deafness.

Intratympanic Injections

The local injection of drugs such as corticosteroids locally, would seem to avoid the series of side effects that lead to suspension of therapy. Even this method of delivery presents different disadvantages, e.g., given its proximity to the round window and the Eustachian tube, it could lead to a residual perforation of the tympanic membrane, but also a series of advantages including an ease delivery of therapy that can be repeated over time e also with

simultaneity between right ear and left ear(De Stefano, Kulamarva, and Dispenza 2010, Dispenza, De Stefano, et al. 2013, Dispenza, Amodio, et al. 2011).

Cochlear Implants

To be evaluated very carefully and after having tried medical therapy according to the various steps. The indication clearly is never given in urgency but assessed over time and varies from case to case.

Table 1. Autoimmune investigation: main complementary 1st-intention examinations

EMS-platelets, PCR, blood ionogram, creatinine, liver tests
CPK, LDH, serum protease electrophoresis, 24-hour proteinuria
Antinuclear factors, native anti-DNA, anti-ENA
Latex-Waaler Rose, circulating anticoagulant, anticardiolipin, C3, C4, CH50
Ophthalmologic examination (including fundus of the eye and research of a sicca syndrome)
Capillaroscopy
Biopsy of accessory salivary glands
X-ray of hands

EMS: blood count; PCR: C reactive protein; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; DNA: deoxyribonucleic acid; ENA: extractable nuclear antigen.

Table 2. Autoimmune investigation: main complementary 2nd-intention examinations

Outside specialized laboratories
HLA typing
Search for an increase in the HSP-70
Ac anticollagene II
Ac antimelin P0
Specialized laboratories
Ac directed against proteins present in large quantities in the cochlea, but not only:
- Ac anti-betatubulin
- Ac anti-lamanina
- Ac anti-Raf 1 protein
Ac directed against proteins present only in the cochlea:
- Ac anti-betatectorine
- Ac anti-coclina

HLA: human leucocyte antigen; Ac: antibodies.

Table 3. Systemic autoimmune diseases associated with autoimmune inner ear disease

Vogt_Koyanagi_Harada Syndrome
Cogan Syndrome
Susac Syndrome
Antiphospholipid syndrome
Rheumatoid Arthritis
Systemic vasculitis
Panarteritis nodosa
Granulomatosis with polyangiitis
Goodpasture Syndrome
Behcet disease
Sarcoidosis
Sjogren Syndrome
Hashimoto thyroiditis
Relapsing polychondritis
Myasthenia gravis
Polymyositis_dermatomyositis
Crohn's disease
Ulcerative colitis
Guillain-Barre' syndrome
Multiple sclerosis

CONCLUSION

ASNHL is a rare kind of sensorineural deafness, difficult to detect and to diagnose correctly. In those patients who suffer from a well-known systemic autoimmune disease, diagnosis is easier and it is supported sometimes by a regression after corticosteroid or immunosuppressive therapies. In patients without a systemic autoimmune disease, the diagnosis is often given when other possible causes are excluded. A medical team made by ENTs, audiologists, rheumatologists, and ophthalmologists is required to manage as well as possible the patient with a suspect of ASNHL.

In order to increase results especially in those patients who can't be delivered with corticosteroid, immunosuppressor and other drugs, local therapies have to be improved. When therapies aren't working, the cochlear implant can be alternatively chosen as a good solution.

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Chapter 64

OCCUPATIONAL HEARING LOSS

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ABSTRACT

Occupational hearing loss is a condition that results from exposure to noise (noise induced hearing loss, NIHL) or to non-noise agents in a work environment. NIHL is usually caused by continuous or intermittent noise exposure which usually develops slowly over several years. Hearing loss from non-noise agents results from exposure to organic solvents, metals, and carbon monoxide. Occupational hearing loss is a prominent global topic affecting individuals, families, businesses and communities, since it is one of the major causes of adult-onset hearing loss at different ages all over the world. Furthermore, occupational noise may have harmful effects eventually independent or associated to hearing loss. Non auditory effects of noise exposure and hearing loss are: physical effects (tinnitus, increased cardiovascular disease risk, fatigue and sleeplessness, increased accident and injury risk, impaired communication), psychological and social effects (annoyance, depression, memory loss, impaired decision making, reduced quality of life, lower confidence and self-esteem, social isolation, relational difficulties) and economic effects (employment and income disruption, increased work absenteeism, increased employee turnover, reduced productivity and performance). Occupational NIHL is typically bilateral, with a classical “notch” at the high frequencies (3000, 4000, or 6000 Hz) and recovery at 8000 Hz, in contrast to presbycusis, indicating a hearing impairment in the middle of the frequency range of human voice. The notch becomes deeper and wider and affects adjacent frequencies in case of continued noise exposure, with a consequent increased impact on speech communications. Making a diagnosis of occupational NIHL is an important step in preventing further hearing loss in the affected

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worker and identifying the potential for NIHL in co-workers. Complete hearing loss prevention programs are needed to effectively reduce the global burden of occupational hearing loss.

Keywords: occupational hearing loss, noise induced hearing loss

INTRODUCTION

Sound is energy in the form of pressure waves that vary rapidly as they move through the air and other media. Sound waves enter the cochlea where they stimulate hair cells (HCs). Such cells convert the vibratory sound energy into electrical impulses that travel via the auditory nerve to the brain, where they are interpreted. In case of HCs destruction, a permanent hearing loss will develop. Sound frequency (pitch) is the number of pressure variations per second and is measured in hertz (Hz). The magnitude or intensity of a sound (loudness) is measured by the sound pressure level in units of decibels (dB). The decibel is used to describe both noise exposure and hearing loss. While sound magnitude is measured as sound pressure level (dB SPL), hearing threshold is measured as hearing level (dB HL).

Averaged thresholds at specific tested frequencies are referred as pure tone average (PTA). The typical pure tone audiometric test includes frequencies at 0.25, 0.5, 1, 2, 4, and 8 kHz, which include the speech frequency range of 0.3 – 4 kHz. Many epidemiological and population-based studies on occupational noise induced hearing loss focus on PTAs that include 0.5, 1, 2, and 4 kHz frequencies.

The perceived loudness of sounds varies with sound frequency as well as with dB level. To account for this, a spectral sensitivity factor (A-filter) is used to weight sound pressure levels to de-emphasise lower and higher frequencies and emphasise the mid-range frequencies to which the human ear is most sensitive (i.e., around the 1–6 kHz range). These A-weighted sound pressure levels are expressed in units of dB(A) [1-3].

Long-term exposure to noise levels beyond 80 dB(A) carries an increased risk of hearing loss, which increases with noise level. Exposure to loud noise is the most common preventable cause of hearing loss and impairment (a weighted average hearing loss at 1, 2, 3, and 4 kHz greater than 25 dB) [4].

Occupational noise hearing loss in workers at different ages accounts for 7% to 21% (mean 16%) of the forms of adult-onset hearing impairment all around the world [5]. Besides hearing loss, occupational noise is associated with tinnitus, cardiovascular disease, depression, increased risk of accidents, and decreased productivity. Occupational hearing loss is a permanent sensorineural hearing loss due to acoustic overstimulation that has the potential for damaging cochlear cells (noise induced hearing loss, NIHL). Occupational NIHL is caused by continuous or intermittent noise exposure and usually develops slowly over several years. However, occupational hearing loss can also result from exposure to non-noise agents, such as chemicals (organic solvents, metals, carbon monoxide) and pharmaceuticals (ototoxins). In case of contemporary causes (i.e., noise and ototoxic chemicals), the effects on hearing loss are usually additive [6]. Many chemicals, either alone or in association with noise, may damage hearing organs and nerves after inhalation or dermal exposure. Potential ototoxic chemicals in the occupational environment are fuels, carbon monoxide, lead and derivatives, toluene, xylene, stoddard solvent, mercury and derivatives, organophosphate

pesticides, chemical warfare nerve agents, perchloro-ethylene, n-hexane, ethyl benzene, trichloroethylene, manganese, styrene monomer, cyanide, organic tin, arsenic, carbon disulfide, paraquat [7].

PATHOPHYSIOLOGY OF OCCUPATIONAL HEARING LOSS

The mechanisms of cochlear damage are mechanical: the exaggerated movements of the basilar membrane cause an increase in oxidative metabolism with a consequent production of free radicals, glutamatergic excitotoxicity, ionic and ischemic disorders responsible for delayed HCs death in the inner ear by necrosis and apoptosis. Increased levels of reactive oxygen species (ROS: molecules or ions formed by the incomplete single-electron reduction of oxygen, superoxide, peroxides, hydroxyl radicals, and hypochlorous acid) and reactive nitrogen species (RNS: nitric oxide-derived compounds that include nitroxyl anion, nitrosonium cation, higher oxides of nitrogen, S-nitrosothiols, and dinitrosyl iron complexes) play a significant role in noise-induced hair cell death [8-10].

Oxidative stress is an imbalance between the production of reactive oxygen species (ROS) and antioxidant defences, potentially resulting in oxidative damage [11]. ROS cause damage by chemically reacting with DNA, proteins, cytosolic molecules, cell surface receptors, and membrane lipids [12] and have been detected in cochlear tissue just after noise exposure [13] just before any morphological sign of damage [14]. The initial mechanical HCs damage occurs in conjunction with transient intense ROS formation; HCs loss progresses over time and stabilizes two or more weeks after the insult when the late formation of free radicals of ROS/RNS causes a delayed HCs loss spreading from the basal turn to the apex [15]. ROS cause the activation of cellular defence pathways such as autophagy [16], a protective process that delivers damaged cellular components to lysosomes for degradation [17]. Such procedure attenuates noise-induced hearing loss (NIHL) by reducing the consequences of oxidative stress [18]. ROS can also cause the production of pro-inflammatory cytokines [19] and tumour necrosis factor [20] which can produce cochlear damage [21]. Calcium homeostasis plays a significant role in regulating ROS release from mitochondria into the cytoplasm [22]. Aminoglycoside antibiotics drastically alter calcium homeostasis by increasing cytoplasmic ROS in HCs; free calcium triggers mitogen-activated protein kinase (MAPK) responsible of HCs damage [23].

Glutamate excitotoxicity is defined as cell death produced by the toxic actions of the essential amino-acid glutamate. Neuronal excitotoxicity is the injury and death of neurons arising from prolonged exposure to glutamate and the associated excessive calcium overload in HCs responsible for the activation of enzymes that degrade proteins, membranes and nucleic acids [24]. High-level noise exposure causes the release of a large amount of glutamate within inner hair cells (IHCs) that overstimulate NMDA receptors, thus producing high intracellular synapses calcium levels. Excessive postsynaptic ion influx into the auditory nerve terminals at the IHCs synapse results in dendritic swelling and vacuolization [25].

In addition, an increased potassium concentration, due to high-level noise exposure, may be toxic for HCs [26] since it increases intracellular calcium concentration which activates a series of enzymes that degrade proteins, membranes and nucleic acids [27].

High-level noise exposure causes cochlear vasoconstriction and reduced inner ear blood flow as well, by means of prostaglandins [28]. Noise-induced ischemia and subsequent re-perfusion further potentiate the generation of ROS [29].

Following intense noise exposure activation of ROS, RNS and MAPK stress pathways, cochlear HCs can undergo apoptosis and/or necroptosis [30-35].

Apoptosis results in the orderly disassembly of cells into membrane-packaged fragments that can be eliminated by phagocytes in a non-inflammatory process. Apoptosis appears extremely rapidly after noise stresses and has been shown to be the primary cell death pathway in the first day following noise exposure [31,32,36]. Necroptosis permeabilizes intra- and extracellular membranes, releasing cellular and organelle contents into the extracellular medium, where they induce inflammation.

Noise exposure has been shown to up-regulate cochlear production of cytokines [20,37] and chemotactic chemokines that attract inflammatory cells to the cochlea [38]. Another potential source of inflammatory mediators is the release of intracellular components into the extracellular environment. Such release develops in case of necrosis or necroptosis, both of which have been implicated in noise-induced cochlear damage [39].

The accumulation of ROS in cells is opposed by the action of native antioxidant enzyme systems, and HCs are no exception to this process. Glutathione, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, glutathione reductase and coenzyme Q10 have all been detected in cochlear tissues [40-42]. These natural defences have to be overcome by ROS before cell damage develops. The antioxidant glutathione in the organ of Corti is distributed in a high-to-low gradient from the apex to the base [43]. This distribution may explain the familiar pattern of HCs damage due to several causes, with initial appearance in the base and progressive extension towards the apex.

CLINICAL AND AUDIOMETRIC CHARACTERISTICS OF NIHL

Occupational NIHL is always sensorineural, typically bilateral. Its first sign is a “notching” of the audiogram on high frequencies (3000, 4000, or 6000 Hz) with recovery at 8000 Hz [44]. This notch typically develops on one of these frequencies and affects adjacent frequencies with continued noise exposure. The exact location of the notch depends on multiple factors including the frequency of the damaging noise and size of the ear canal. In early NIHL, the average hearing thresholds at the lower frequencies (500, 1000, and 2000 Hz) are better than the average thresholds at 3000, 4000, and 6000 Hz, and the hearing level at 8000 Hz is usually better than the deepest part of the notch. Noise exposure alone usually does not produce a loss greater than 75 dB at high frequencies and greater than 40 dB at lower frequencies. Hearing loss due to noise exposure increases most rapidly during the first 10 to 15 years of exposure, while the pattern of hearing loss decelerates later on: previously noise-exposed ears are less sensitive to future noise exposure. Furthermore, it is unlikely that NIHL progresses if noise exposure is discontinued.

The presence of a temporary threshold shift (TTS: the temporary loss of hearing, which largely disappears 16–48 hours after exposure to loud noise) with or without tinnitus is a risk indicator that permanent threshold shift (PTS) will occur if hazardous noise exposure continues. Except for ototraumatic accident, workers always develop TTS before sustaining PTS [45].

When evaluating cases of asymmetric loss, a referral to rule out a retrocochlear lesion, such as an acoustic neuroma, is required before attributing the loss to noise. The addition of very intense and frequent impulse/impact noise to steady-state noise can be more harmful than steady-state noise of the same A-weighted energy exposure. There are a number of other causes of sensorineural hearing loss besides occupational noise. These include non-occupational noise exposure (recreational noise), exposure to ototoxic compounds including drugs [46,47], mutations in deafness genes [48-51], infections such as labyrinthitis or prenatal cytomegalovirus [52-56], aging [57,58], head injury, therapeutic radiation exposure, neurologic disorders, cerebral vascular disorders, immune disorders, bone diseases (Paget disease), central nervous system neoplasms, and Ménière disease [59].

NIHL is irreversible. Detection and intervention are critical to prevent this condition to develop. A significant threshold shift (STS) of 10-dB from the baseline in PTA at 2000, 3000, and 4000 Hz is an important early indicator of permanent hearing loss [60]. TTS is an important early and reversible indicator that potential cochlea HCs damage can progress to a STS. Tinnitus is another early warning symptom for NIHL [61-64]. One of the main components of the hearing conservation programme is the annual pure tone audiogram (PTA), designed to detect workers with NIHL early and to submit them to subsequent interventions that might arrest hearing loss progression. The use of PTA at 2, 3 and 4 kHz has shown the highest sensitivity and specificity amongst the other pure tone averages [65].

Otoacoustic Emissions (OAEs) are an important technological advance in audiological assessment. OAEs are sounds produced by the cochlea, specifically the outer hair cells (OHCs), and measured in the outer ear canal. Transient Otoacoustic Emissions (TEOAEs) are evoked responses from stimulating the cochlea with a transient signal such as a click or tone burst acoustic signal. TEOAEs are a wide frequency response in 500 to 5000 Hz range. Distortion Products (DPOAEs) are evoked response OAEs from stimulating the cochlea with two simultaneously presented pure tones of different frequency. This type of OAE can be recorded in individuals with a more severe hearing loss, at higher frequencies with more frequency specificity. DPOAEs are obtainable in the frequency range of 500 to 8000 Hz. They typically do not occur in hearing losses greater than 30 dB. The production of OAEs by the OHCs of the cochlea is due to the cochlear active processes. In case of OHCs damage producing a mild hearing loss, OAEs are not present.

OAE testing is twice as sensitive as audiometry to detect a change in hearing threshold level and could improve monitoring for noise-induced hearing loss in the workplace [66]. Furthermore, OAEs indicate noise-induced changes in the inner ear undetected by audiometric tests [67]. More studies are needed to show whether OAE testing can replace standard audiometry or whether the two techniques have complementary roles.

NON AUDITORY EFFECTS OF NOISE EXPOSURE

Occupational and environmental noise exposure may have important non-auditory effects, eventually independent or associated to hearing loss. Such effects can be manifold, bothersome and, sometimes, serious.

Among them, tinnitus is one of the most frequent and annoying. It can have low intensity or can be extremely severe, thus causing distress, depression and sleep discomfort [68,69].

Environmental or occupational exposure to noise can have effects on the cardiovascular system, causing tachycardia and high systolic and diastolic blood pressure, in addition to other risk factors such as blood lipid concentration, blood viscosity and blood glucose concentration [70-74]. Chang et al. (2013) [75], found that high noise exposure (≥ 85 dBA) increased systolic pressure by 3.2 mm Hg and diastolic pressure by 2.5 mm Hg. Such conditions can increase the risk of severe events such as myocardial infarction and stroke (Basner et al., 2014). Potential mechanisms are emotional stress reactions with release of catecholamines and glucocorticoids (indirect pathway) and non-conscious physiological stress from interactions between the central auditory system and other regions of the CNS (direct pathway) [76-78].

In 2009, WHO published the Night Noise Guidelines for Europe, an expert consensus that mapped four noise exposure groups to negative health outcomes ranging from no biological effects to increased risk of cardiovascular disease (below 30 dB_{aeq,night,outside}; 30-40 dB; 40-55 dB; above 55 dB_{aeq,night,outside}: in this group the situation is considered increasingly dangerous for public health [76].

Exposure to loud noise has been linked to adverse psychological and social effects. It can cause anxiety, depression, annoyance, sleeplessness [79]. Particularly, sleep disturbances are thought to be one the most deleterious non-auditory effect of environmental noise exposure, since a sufficient undisturbed sleep is considered necessary for a good quality of life [80]. The effects of environmental noise exposure depend not only on the acoustical properties of the sound [76] but also on the momentary sleep stage [81] and individual noise susceptibility [82]. Elderly people, children, shift-workers and people with a pre-existing sleep disorder are thought to be the major risk groups for noise induced sleep disturbance [76-78].

Other authors reported negative effects of chronic noise exposure on memory (IEH, 1996) [83], decision-making ability [84] and after-work irritability [85]. Many studies demonstrated environmental noise exposure has a negative effect on children's learning outcomes and cognitive performance [86]. Postulated mechanisms for these effects are communication difficulties, impaired attention, increased arousal, learned helplessness, frustration, noise annoyance and consequences of sleep-disorders [76].

Recently, Sorensen et al. (2014) [87] have shown a relation between exposure to traffic noise and post-menopausal breast cancer, while some other authors have demonstrated the association between noise exposure and obesity [88,89].

Many of these conditions seem to be associated with a higher frequency of workplace [90,91]. In conclusion, the consequences of chronic noise exposure have a significant social cost, since they are associated with a high frequency of working days loss and reduced productivity [92, 93].

According to the WHO, more than one million healthy life years (disability adjusted life years, DALY) are lost annually in the European Union because of community noise exposure. Noise-induced sleep disturbance is responsible for about 900.000 DALYs, annoyance for 650.000, ischemic heart disease for 65.000 and children's cognitive impairment for 45.000 DALYs [94].

INNER EAR PROTECTION FROM NOISE

Occupational NIHL is permanent. At the moment, no effective treatment to regenerate damaged sensory receptors after noise exposure has been reported, leaving amplification as the only option. However, the risk of NIHL can be greatly minimized if noise is reduced to below 80 dB(A) [95].

The maximum daily occupational noise exposure level at an eight-hour equivalent continuous A-weighted sound pressure level is 85 dB(A). The preferred solution to excessive noise exposure is to completely eliminate the source of loud noise. When this is not possible or practical, the legal requirement is to minimise exposure through a hierarchy of controls: substitute the noise source with quieter machinery or processes, isolate the noise source from workers, apply engineering solutions and install noise guards or enclosures, apply administrative solutions, provide signs and quiet areas for breaks, and when none of the above are reasonably practicable, provide personal hearing protectors (e.g., ear muffs and plugs).

The high rate of occupational NIHL casts doubts upon the effectiveness of prevention programs or people's compliance to them. The average hearing loss prevention programs show the poor effectiveness of non-pharmaceutical interventions for preventing occupational noise exposure and occupational NIHL and do not reduce the risk of hearing loss to below a level at least equivalent to that of workers who are exposed to 85 dB(A) [96].

There are two therapeutic strategies to reduce cochlear damage in NIHL: inhibit pathways that lead to the damage of HCs and enhance processes that enable HCs survival. Antioxidants protect HCs and hearing from noise induced noise [97-100].

The antioxidant N-acetyl cysteine (NAC) in military trainees showed some degree of protection [101] in contrast to other studies, where no protective effect of NAC was found during stapes surgery [102] and on TTS induced by loud music [103].

Reduction of inflammation also has the potential to protect against NIHL: steroid dexamethasone, delivered to the round window membrane, has also been shown to reduce hearing loss after noise [104]. The patients suffering from recently NIHL receiving intratympanic treatment showed significantly more improvement in thresholds than patients receiving systemic steroid alone [105]. Delivery to the inner ear across the round window membrane into the perilymph provides the possibility to utilize a wider variety of potential therapies for inner ear protection from noise.

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Chapter 65

SINGLE SIDE DEAFNESS IN CHILDREN

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ABSTRACT

The importance of a good hearing function to preserve memory and cognitive abilities has been shown in the adult population but studies on the pediatric population are currently lacking. To date we have investigated memory and cognition; Memory was studied in children affected from Single Side Deafness (SSD) and treated with Bone Anchored Hearing Implant (BAHI) while the cognition was studied in a sample of children affected from Unilateral Asymmetric Hearing Loss (UAHL) evaluating the effect of Adhesive Anchored Prosthesis (AAP). Both studies aimed evaluating the effects of BAHI or AAP on speech perception, speech processing, and memory in children with SSD or UAHL. We enrolled in the two studies a total of 35 children (25 with SSD and 10 with AUHL) and assessed them prior to BAHI implantation or AAP use. In the case control study (BAHI) children were evaluated at 1-month and 3-month follow-up using tests of perception in silence and perception in phonemic confusion, dictation in silence and noise, working memory and short-term memory function in conditions of silence and noise. We also enrolled and evaluated N = 15 children with normal hearing. In the AUHL study, instead, we evaluated speech perception test, dictation test, working memory and short-term memory function tests prior to the intervention (no Hearing Aid (NoHeAi)), immediately after the intervention (AAPT0), and 1week post-intervention (AAPT1).

Keywords: single side deafness, hearing loss, bilateral hearing

In the BAHI study we found a statistically significant difference in performance between healthy children and children with Single Side Deafness (SSD) before BAHI implantation in the scores of all tests. After 3 months from BAHI implantation, performance of children with SSD was comparable to that of healthy subjects in speech perception, working memory and

short-term memory function in silence, while differences persisted in the scores of the dictation (both in silence and noise condition) and working memory function test in noise condition.

The AAP study showed at AdHeT1 statistically significant improvement compared to their pre-intervention baseline (NoHeAi) in speech perception ($p = 0.01$) and dictation ability both in noise ($p = 0.03$) and silence ($p = 0.02$) conditions. Scores of the short-term memory test ($p = 0.01$) and of the working memory test in noise ($p = 0.01$) and silence ($p = 0.01$) conditions were also improved. Similar results were obtained for subjects with mild and severe SSHL. At AdHeT0 subjects showed an improvement in the scores of all tests compared to NoHeAi, but the changes were not statistically significant.

Our data suggests that in children with SSD BAHl improves speech perception and memory; the AAP might be helpful in the treatment of AUHL for the same reason of BAHl in SSD. Speech rehabilitation may be necessary to further improve speech processing both with BAHl that with AAP.

INTRODUCTION

The importance of recovery of bilateral hearing function is a widely accepted concept in the treatment of patients with bilateral deafness[1]; conversely, single side Hearing Loss (SSHL) are rarely treated with hearing aids [2], bone anchored hearing aid [3], or cochlear implants (CI) [4]. In patients with SSHL, both adult and pediatric, a good unilateral hearing function is typically considered acceptable, and the option of using a hearing aid is often underexplored. However, bilateral hearing function is not only important for hearing correctly, but it is also necessary for identifying origin and direction of sound [5], perceiving nuances of music [6], and improving the hearing ability function in noise situations [3, 4]; in children, it is key for developing normal auditory pathways [7]. As it has been shown by recent studies, bilateral hearing improves quality of life, social life, speech perception [8], and memory function [8-11]. While most studies focus on assessing these outcomes in CIs recipients [4, 8, 9], the effects of hearing aids and bone anchored systems are rarely studied [14].

Recently it was demonstrated on adult population that working memory performances are influenced by hearing function [14-16]. In fact it has been shown that hearing impairments affect working memory function in subjects who are asked to identify spoken sentences with semantic ambiguity [14, 15]. Increased auditory thresholds decrease scores in the Text Reception Threshold test [17, 18] which suggests that hearing impairments also ultimately affect reading performance. Finally, in a recent study, Saunders et al. showed that improvement in hearing via a personal frequency modulation system led to an enhancement of word recognition ability in veterans [19].

The link between hearing impairment and working memory shown by the aforementioned studies is not surprising. In fact, working memory which is part of the short-term memory and whose main role is managing the information temporarily stored in the short-term memory, is composed of four main parts, one of which (phonological loop) is specifically dedicated to storing and manipulating verbal information [20]. The phonological loop works in synergy with the central executive (an attentional control system), the episodic

buffer [21], and the visuospatial sketchpad (useful for visual and spatial information) for ensuring a correct higher-level processing of verbal data, such as word recognition, reading, and speech production.

While current literature on the relationship between hearing abilities, memory and speech processing mainly focuses on adults, studies on the pediatric population are lacking. In particular, little is known on how hearing abilities affect memory function in children with Single Side Deafness (SSD). Understanding this relationship in this population is particularly important as both these functions affect learning, and thus potentially academic performances.

HOW TO TEST AUDITORY AND MEMORY

The screening tests for children affected from Single Side Deafness (SSD) includes auditory test and study on memory functions.

During each evaluation session, all subjects undergo tests for evaluating speech perception, memory (working memory and short-term memory), and dictation performances. Speech perception is evaluated by using the Common Evaluation Protocol in Rehabilitative Audiology (CEPRA) [22], where we evaluate Perception in silence (PS) and Perception in Phonemic Confusion (PPC), also evaluated in silence condition.

The PS test allows an integrated evaluation of hearing and brain function (working memory), while the PPC test allows a mere evaluation of the actual hearing ability (sounds perception) [22].

Working memory and short-term memory are evaluated respectively with the non-sense word repetition test and the verbal span test, both from the PROMEA battery of tests [22]. In the non-word repetition task, the assessor read aloud a list of forty non-sense words of different length. The subject was asked to listen and repeat each word. The total test score was calculated as the number of correct words. The verbal span test included six lists of words of different frequency of use, length, and level of similarity. Each list was composed of seven blocks of word sequences and each block identifies a different span level (from 2 to 8). The subject was asked to repeat the sequences read by the assessor maintaining the same words order. The span level corresponded to the highest number of words correctly repeated in at least three sequences out of five. Working memory tests were performed in silence (WMS) and noise (WMN, cocktail party noise) conditions [23, 24]. Short-term memory (SM) tests were performed in silence condition. The dictation tests were taken from DDE-2 test [23], and tested overall speech recognition ability including hearing function, short term memory, working memory, signal integration, and writing skills; they were performed in silence (DS) and noise (DN) conditions. The stimuli included non-sense words. In the tasks the examiner read 24 non-sense words, one by one. The subject was asked to repeat each word aloud and write it down.

STUDIES RESULTS

We completed two different study to investigate the effect of bilateral hearing restoration on working memory function by using bone adhesive prosthesis (AAP) and bone anchorage

hearing implant (BAHI); the first was a cross-sectional pilot study in which we analyzed children without and with AAP for evaluating the variance in working memory performance, then in the second one we compared the working memory performance between children with SSD with and without BAHI and a group homogeneous for age and sex of healthy children.

In the first study we observed that all children showed an improvement in speech perception and dictation, short term and working memory function tests when we compared their performance without hearing aids and with AAP. The study analyzed the use of AAP at two different times, when children used AAP for a day only and when they used it for a week at least. In all cases (single day and one week) children improved their performance.

We observed that in single day use of AAP, children improved 15% and 32% their dictation performance, respectively in silence and noise. The working memory scores were better than without hearing aids both in silence (25% of gain) and in noise (40%). The short memory notably improved when children used AAP (22% of gain).

After 1 week of constant use of AAP every day, children improved their performances in dictation test of 40.3% when they used AAP, specifically they gained a 31% in silence condition until a 51% of improved performance in noise.

We observed that the working memory scores improved by 33% in silence and 58% in noise when children used AAP; short term in particular improved 17%.

In the second study we compared the performance of children with SSD with a healthy group, without and with BAHI; we studied as the first study, the speech perception, the dictate ability and the working memory.

Children with SSD presented statistically significant difference when compared with the healthy, in all tests when they did not use the BAHI. These differences completely disappeared when children used BAHI and in this way the bilateral hearing function was restored.

The only test in which we did not observe equal performance after use of BAHI was the dictation, in fact even the children with BAHI really improved their performance when compared with themselves with single hearing function, the recovery was not big enough to pair with the healthy children.

DISCUSSION

The overall results of our studies, showed that a bilateral hearing function is fundamental to reach good performance in speech perception, dictate test and working memory function.

In fact, both patients with AAP and the ones with BAHI really ameliorated their personal performance when the prosthesis was applied on the SSD ear, by supporting the idea that also in presence of good function of a single ear the bilateral hearing function have to be always searched, in fact authors have been shown that in pediatric subjects even a mild loss of hearing function can trigger fatigue and ultimately reduce subjects' academic performance [26], as well as reduce intellectual abilities [27].

In our first study patients using AAP showed an overall improvement in speech perception, dictation, and working memory tests; improvements tended to increase with prolonged use (7 days) of the prosthesis.

In the speech perception test, all subjects displayed an improvement with AAP when compared with no use of hearing aids. The improvement in this test was, however, smaller compared to the improvements in the other tests.

The dictation was improved also by analyzing performance after 1-day use of AAP even obviously the major increasing of the performances was observed after 1 week of AAP use.

Memory abilities largely improved with use of AAP, both in terms of working memory and short-term memory. The working memory, a part of short-term memory, is the cognitive function involved in manipulating the information temporarily stored in the short-term memory. According to the multi-component model of Baddeley and Hitch [20] working memory can be divided into the following components: 1) phonological loop, which stores and manipulates verbal information; 2) visuospatial sketchpad, useful for visual and spatial information; 3) the central executive, that works as an attentional control system, and at least 4) the episodic buffer. The episodic buffer component stores information from the subsystems in a multimodal code and combines it with information from long-term memory into a unitary episodic representation [21]. The fact that subjects improved in both memory and dictation tests is not surprising, as a short-term and working memory amelioration not only enhances the quantity of storable information, but also facilitates data manipulation and translation from the phonological to the graphemic code.

The biggest gain in working memory function was achieved at after 1 week of use of AAP when the children were tested in the noise and silence conditions. The improvement in silence condition was smaller than the one in noise. After 1 week of AAP use, short term memory function was also greatly improved, and displayed a trend in improvement similar to the one observed for working memory.

These results are on line with the several studies that have shown how the bilateral hearing function is fundamental for maintaining good memory function [27-29], verbal abilities [30, 31, 32], and word recollection performance [33]; all these functions require the ability to identify and recall sounds in the voice frequency band [27].

In our second study, we reinforced the results obtained in the first one, in fact we observed a statistically significant difference between children with SSD without BAHI and healthy controls, in speech perception, dictate test and working memory function.

We chose to measure subjects' performance in speech perception, dictation, and working memory function tests as these skills are known to be related.

When children with SSD used BAHI, they displayed impaired performance compared to healthy subjects only in the dictate and working memory tests in noise, all other scores instead were similar to those recorded from the control group.

The comparison between subjects with SSD using BAHI and healthy controls did not show a statistically significant difference for speech perception both in silence and in noise, indicating that BAHI improves speech perception ability in terms by improving subjects' ability to perceive sound [25, 34].

The dictation abilities of children with SSD using BAHI, although improved when compared to not use of hearing aids, did not reach results statistically significant enough for defining a performance that was the same of the healthy.

We think that this result may be due to a combination of the complexity of the dictation test and the relatively short follow-up we used in this study. Multiple abilities are required to reach high scores in a dictation test, including good hearing function, concentration, short-

term memory, and overall confidence of being able to complete the task. Re-acquiring all these skills may take time, possibly longer than the 3 months of our observation period [22].

We investigated working memory both in silence and noise condition to assess the effect of environmental conditions [35]. Children with SSD using BAHI showed performance similar to the healthy for working memory in silence and short memory; the gain that they have had in working memory performance in noise comparing SSD without BAHI and with BAHI, was not big enough to reach the same performance of the healthy. The difference we observed in the working memory in noise scores might be due to the fact that BAHI increases sound perception; as previously shown by other authors [9-14, 19], this increase can cause difficulty in concentration, especially if subjects perceive the noise as meaningful [36].

The key role of bilateral hearing function in preserving good memory function [10, 27, 37-39], verbal abilities [27, 28], and word recollection performance [29] has been shown by a number of studies; all these functions require the ability to identify and recall sounds in the audible frequency band [35]. Our results show that even children who preserved good unilateral hearing function can benefit from the use of BAHI, and that bilateral hearing function positively affects memory function [10, 32, 36, 40]. The bilateral hearing function gained through BAHI allowed SSD children to achieve speech perception abilities comparable to those from healthy subjects in the same age range as well as similar results in terms of short-term memory and working memory function in the noise condition. Performance in the dictation and working memory tests of children with BAHI might be further improved by speech rehabilitation.

CONCLUSION

The results of our studies confirm that bilateral hearing function needs to be achieved always, even in case of quite satisfactory quality of life with a single

The effect of bilateral hearing improves not only the speech perception but also superior brain function.

It is known that in case of deafness there is not a re-organization of brain area, in opposite to that happen in blindness, but we still don't know what happens in SSD

Our results showed that by using AAP of BAHI the performances of children affected by SSD become similar to the healthy ones in the same age range.

In our opinion SSD or asymmetric hearing loss (HL) should be treated with hearing aids, in case of SSD and severe form of HL, BAHI is the more appropriate technology. In case of mild and mild to severe HL the AAP is the best solution, because is a minimally invasive high-performance system.

Anyway, speech rehabilitation after BAHI implantation or AAP application might help fill the gap in performance between subjects with SSD and healthy controls and help the former to achieve full recovery of complex functions such as those required by the dictation and working memory tests in noise condition.

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Chapter 66

PHARMACOLOGICAL TREATMENT OF SENSORINEURAL HEARING LOSS

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ABSTRACT

Sudden sensorineural hearing loss is a common and alarming symptom of about 360 million people that suffer from hearing impairment worldwide. The sudden sensorineural hearing loss usually arises unilaterally and it is habitually described as greater than 30dB hearing reduction, attributable to lesions of the cochlea, cranial nerve VIII, brainstem and temporal lobe. There are many factor that promote the onset of this lesions such us infections, circulatory diseases, inner ear neoplasia and neurological disorders. This pathology is characterized by primary symptoms such as the impairment of the comprehension of spoken language and the struggling to listen to music. Subsequently, secondary symptoms arise as well as anxiety, inadequate coping with illness and psychosomatic disturbances that have a negative impact on patients with a significant reduction in the quality of life. Treatment of the sudden sensorineural hearing loss remains one of the most problematic issues for contemporary otorhinolaryngology,

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because of the wide array of the presumed mechanisms that underpin this disorder. Although the pharmacological treatment remain even now empirical and the management is not standardized in term of medical treatment, duration and route of administration, different agents are used. In the past, pharmacological approaches have included antiviral agents, vitamin, herbal preparations, carbogen inhalations or magnesium, administered on either an inpatient or outpatient procedures. Nowadays, the corticosteroids therapy remains the mainstay strategy, but considering the multifaceted aspects of this disorder, diuretics, anticoagulants, vasodilators and fibrinolytic agents have also been tried. In this chapter, we will focus mainly on the principal pharmacological approaches of the sudden sensorineural hearing loss that will be described and examined in terms of mechanism of action and effectiveness.

Keywords: sudden sensorineural hearing loss, glucocorticoids, prostaglandine E1

INTRODUCTION

Hearing well is synonymous with living well. A high quality of hearing reflects a fully participation in everything that happens around us, in fact, hearing is the sense that receives sounds which come from outside the human body, transmitting them, through complex mechanisms that originates in the auricle, in the temporal cortex, the area of the brain able to receive and decode sounds.

The correct functioning of the hearing system has a positive effect also at cognitive levels; in fact, there is a direct correlation between hearing loss and ability of the brain to process information and recall memories.

Given the importance of correct functioning of the hearing system, appear clear how troubled and disabling could be a total or partial perceptual hearing loss.

The Sudden Sensorineural Hearing Loss (SSHL), defined by US National Institute for Deafness and Communication Disorders (NICDC) as an idiopathic loss of hearing of at least 30 dB, nearly always unilateral, is one of the most common human ailments and the most ordinary complaint of patients evaluated by hearing impairment specialists. It occurs at any age making verbal communication and comprehension of spoken language more difficult. Usually patients notice that the hearing loss appears instantaneously in the morning even if others describe that it rapidly developed over a period of hours or days [1].

The onset of the symptoms is subjective, but generally it occurs over less than a 72-hour period and the severity of the harm also varies from patient to patient [2].

SSNHL affect the inner ear and the neural pathways to the auditory cortex. Although the pathology predominantly affects adults, children also can be affected [3].

The diagnosis of deaf patients is difficult and impose a specify analysis of the primary symptoms such as impairment of the localization of sound, the difficulty on comprehension of spoken language in a noisy environment, and the enjoyment of music. These symptoms are frequently associated with secondary symptoms as anxiety, inadequate coping with illness, various types of psychosomatic disturbance, and damage quality of life [4]. Considering the multifaceted aspects of the SSNHL, such as patient age, presence of vertigo and/or tinnitus at onset, exposure to ototoxic agents, degree of hearing loss, audiometric configuration, time between onset of hearing loss, and co-morbidities such as hypertension and diabetes, treatments have traditionally been empirical [5-9].

Corticosteroids, *via* systemic and/or intratympanic administration, have been the most commonly agents used to treat SSNHL, even if a large array of other drugs, such as antivirals, antibiotics, diuretics, vasodilators, osmotic agents, plasma expanders, anticoagulants, mineral supplements, and hyperbaric oxygen or carbon dioxide rich gases, among others, have been used [10].

Although the etiopathology of this disease is still unclear, this chapter aims to understand the pathophysiology and the appropriate drug therapies, by answering four simple questions: *What is Sudden Hearing Loss? What Causes Sudden Hearing Loss? How is Sudden Hearing Loss Diagnosed? How is Sudden Hearing Loss Treated?*

SUDDEN SENSORINEURAL HEARING LOSS: INTO THE MEDICAL HISTORY

SSNHL, described as a medical emergency in search of appropriate diagnostic techniques and treatments, is generally defined as a rapidly developing hearing loss with a threshold reduction of ≥ 30 dB in at least three contiguous audiometric frequencies [11].

According to the World Health Organization, about 360 million people suffer from hearing impairment worldwide and in the European Union, the number is expected to amount to 434,000 people suffering from deafness and 44,000,000 people suffering from hearing impairment [12, 13].

All ages and both sexes are affected, with peak ages ranging between 30 and 60 years [14, 15]. According to the otolaryngologist guidelines, SSNHL is a suddenly appearing, generally as an unilateral hearing loss of cochlear origin with unknown cause (i.e., idiopathic), expressing different degrees of severity, up to complete deafness (*anacusis*), sometimes additionally with vertigo and/or tinnitus [16].

The SSNHL etiology remains unknown in the most of patients and the causes can be numerous and could be congenital or acquired [Table 1]. Although the list of potential etiologies is lengthy, the more substantial evidence seems to support that SSNHL is most commonly the result of viral infections, vascular disruption, inner ear problems, such as Meniere's disease, neoplastic, traumatic, metabolic, neurologic and cochlear injuries and also autoimmune processes, toxic damage and alcohol use. None of these etiologies has undisputed evidence supporting its role in the cause of SSNHL, therefore, these cases remain idiopathics [17-19].

Regarding its pathophysiological, still unclear, three major categories of hearing loss could be considered to the differential diagnosis: the impeded sound conduction through the external ear, middle ear or both; hearing loss that occurs within the cochlea or the neural pathway to the auditory cortex; and eventually a mixed hearing loss, concomitant with a conductive loss and sensorineural one [20].

Generally, SSNHL has a rapid onset, occurring over a 72-hour period, of a subjective sensation of hearing impairment in one or both ears. It indicates an abnormalities of the cochlea and auditory nerve, with negative impact to the central auditory perception or processing. The most frequently used audiometric criterion is a decrease in hearing and since premorbid audiometry is generally unavailable, hearing loss is defined as related to the opposite ear's thresholds [21].

But *what should we take account of SSNHL?* The majority (96–99%) of sudden hearing loss is unilateral [22, 23]. Causes of bilateral sudden hearing loss are due to autoimmune diseases, syphilis, especially if rapidly progressive, and it occurs commonly in older patients with pre-existing diabetes mellitus and lipid abnormalities. Therefore, it is relevant a full medical history. Detailed otolaryngological experiences indicate that prognosis for recovery is dependent on other factors, including patient age, degree of hearing loss, audiometric configuration, time between onset of hearing loss and treatment, and also presence of vertigo or tinnitus at onset [24, 25].

Table 1. Etiological Factors for Hearing Loss

Infection	Meningitis (bacterial, fungal), labyrinthitis (bacterial, fungal, viral, parasitic, spirochaetal), mumps, measles, chicken pox, syphilis.
Congenital	Large vestibular aqueduct, Mondini dysplasia.
Traumatic	Head injury (with or without fractures), barotrauma (with or without perilymphatic fistula), acoustic trauma, iatrogenic injury.
Neoplastic processes	Vestibular schwannoma and metastases of the meningeal temporal bone, leukemia, multiple myeloma.
immunological disease	Systemic lupus erythematosus, Cogan syndrome, Wegener's granulomatosis.
Ototoxic agents	Medical product, drugs, tissue toxins
Vascular disease	Hypertensive crisis, hypotonia, AICA (anterior inferior cerebellar artery infarct) infarction.
Neurological diseases	Neurofibromatosis type II, multiple sclerosis, focal ischemia pontine.
Metabolic disorder	Iron metabolic disorder, renal failure/dialysis.

Tinnitus, defined as an abnormal noise perceived in one or both ears or in the head in which a patient has a conscious hearing percept in absence of external sound, is usually reported in patients with SSNHL [26-28]. Given the considerable correlation between tinnitus and sudden hearing loss, studies have been reported that the incidence seems to be 5-30 per 100,000 persons per year [29, 30] and accounts for 1% of all sensorineural hearing loss cases [31].

SSNHL commonly occurs in patients aged between 25 and 60 years old, with a peak in prevalence for patients between 46 and 49 years old with increasing incidence with age and male are equally affected as females [32-34].

Although SSNHL has a greater impact on adults, it also affects children, but it is very rare and its cause is still unclear. It has been reported that 6.6% of patients with SSNHL were under 18 years of age, 3.5% under 14 years, and only 1.2% under 9 years [35]. Due to the rarity of SSNHL in the pediatric population, research regarding etiology, treatment outcomes and prognosis of SSNHL in children is limited.

SYMPTOMS: FROM THE MECHANISTIC DAMAGE TO THE DISTORTED PERCEPTION

Sound waves are conducted via the external ear and the external auditory canal to the tympanic membrane. The mechanical vibrations are transmitted by the ossicles way of the middle ear to the cochlear perilymph and endolymph. Thus, all the disturbances that arise

along the sound conduction pathway, have a mechanical nature that terms into a hearing loss [36].

People who get a hearing loss, usually refer a reduction in hearing ability, describing the feeling that have hair in the auricle or a large wool pad into the ear canal.

The subsequent *hyposcousia* has also a perceptive nature, since the inner ear (cochlea, acoustic nerve) cannot transmit, through the central acoustic way, the correct nervous impulse from sound vibrations [37]. This results in a distorted perception of sounds, impairment of the comprehension of spoken language and the struggling to listen to music. In fact, people often compensate to the hearing impairment by turning up the volume of the radio or television set, or (in unilateral hearing impairment) by turning the healthy ear to the sound sources.

In addition to a great insecurity among people affected, toward the environment, it is very common taking advantage from vision to speech recognition with an increasing reliance on lip-reading, in order to prevent the consequent inappropriate answers to misheard questions and an excessively loud speaking voice.

But the simultaneous presence of other symptoms, makes the sudden hearing loss even more disabling. In fact, patients often report disorders such as vertigo, tinnitus and buzzing and just about to the numerous symptoms reported, experts' opinions about causes and therapies are enough controversial [38].

DIAGNOSTIC MEASURES: THE STATE OF THE MULTIPLE EVIDENCES

SSNHL defined as a rapid onset, occurring over a 72-hour period, of a subjective sensation of hearing impairment in one or both ears, has a sensorineural nature and meets audiometric criteria. The most frequently used audiometric criterion is a decrease in hearing of ≥ 30 decibels (dB), affecting at least 3 consecutive frequencies. Because premorbid audiometry is generally unavailable, hearing loss is defined as related to the opposite ear's thresholds. [39]

Although patients often underestimate a tangible disease, clinical experiences indicate that a range from 32% to 65% of cases of SSNHL may recover spontaneously [40, 41].

Many of the discoverable causes of SSNHL induce permanent hearing loss due to the damage to hair cells or other inner ear structures. Prognosis for recovery depend on a several number of factors, in fact, the evaluation usually lay the groundwork for a careful history on physical examination, beginning to patient age, presence of vertigo or tinnitus at onset, degree of hearing loss and time between onset of hearing loss [5,42]. Moreover, it is essential looking for potential infectious causes such as otitis media, systemic diseases and exposure to known ototoxic medications.

Given the decline in hearing, the first step to diagnose the SSNHL, usually requires an audiogram.

Instead, blood studies are usually performed to rule out potential systemic causes (i.e., syphilis, Lyme disease, metabolic, autoimmune and circulatory disorders) [43]. Moreover, in order to investigate the presence of acoustic neuroma, which is reported to be existent up to 15% of patients with sudden hearing loss, Magnetic Resonance Imaging of the brain is frequently recommended [44].

Considering the large amount of etiological causes, the different and usual procedures, required in individual cases, are reported in Table 2.

Table 2. Diagnostic Measures

Otoacoustic emissions (OAE)
Auditory evoked brainstem potentials (ABR)
Speech audiometry
Stapedius reflex measurement
Functional examination of the cervical spine
Laboratory tests: blood glucose, CRP, procalcitonin, small blood count, differential blood count, creatinine, fibrinogen level
Serologic testing: borreliosis, syphilis, herpes simplex virus type 1, varicella zoster virus, CMV, HIV.
MRI: exclusion of a tumor of the cerebello pontine angle
CT scan: skull, temporal bone, cervical spine
Electrocochleography: coclear damage, exclusion of hydrops
Auditory steady state responses (ASSR)
Tympanoscopy

**PHARMACOLOGICAL MANAGEMENT:
GLUCOCORTICOIDS MECHANISMS OF ACTION**

Numerous agents have been suggested and used to treat of the SSNHL, in concert with alternative approaches (i.e., acoustic, electrical, surgical and radiological strategies). A large number of different drugs have been investigated for the treatment of idiopathic SSNHL including antiinflammatory agents, antimicrobials, calcium antagonists essential minerals, vasodilators, volume expanders, defibrinogenators, diuretics and hyperbaric oxygen [41]. On the basis of the etiology of this disorder, still unclear, there are insufficient evidences supporting the daily application of antiviral, vasodilatory or antioxidant drugs, together with alternative therapeutic methods, which also include vitamins or Ginko Biloba [45, 46].

The most common approach to treatment of SSHL is with glucocorticoids (GC), which are considered, around the world, to be the gold standard of therapy, because it is thought the disorder might be due to an infectious/inflammatory or autoimmune process [4, 47]. GC act on almost all organs, mainly carrying out their effects through a DNA-mediated induction of protein biosynthesis after transformation of an intracellular GC receptor (GCR). In the cytoplasm, the non-active receptor is present in a complex with chaperones. The GC-activated GCR undergoes an initial conformation change, resulting in the dissociation of the chaperone–GCR complex. In this way the GC–GCR complex is activated and can translocate to the nucleus where it dimerizes. As a homodimer, it can bind to the DNA regulatory sequences, called GC response elements (GRE) and found in the promoter regions of glucocorticoid-regulated genes. If the GC–GCR complex binding leads to gene activation, the GRE sequence termed as ‘positive’ GRE. Negative GRE is also described where GC–GCR leads to gene suppression (direct repression) [48, 49]. GCs action includes their influence (direct or indirect) on the human genoma (DNA within the nucleus) transcription and translation, for many genes encoding inflammatory mediators. Its actions become evident within 1 to 2 hours and the cytoplasmatic effects, mostly at very high doses, occur after only a

few minutes [50]. Each cell contains 2 classes of GCR, type I (glucocorticoid) and type II (mineralocorticoid), both of which are present in the cochlear and vestibular tissues of mammals [51, 52]. The activation of cytoplasmatic GCR lead to the triggering of transcription processes and also the expression of specific genes, that inhibit the synthesis of inflammatory mediators and cytokines, which are responsible for the anti-inflammatory effects of GC. GC also affect carbohydrate and protein metabolism and change the physicochemical characteristics of cell membranes, promoting their stabilization and reducing the permeability of cations (cytoplasmic effect). Finally, they are able to regulate cellular osmolarity through the binding of type II mineralocorticoid receptors, which activate the enzyme Na,K-ATPase [53]. This enzyme is found at the base of the external and internal hair cells, the tympanic nerve fibers and the spiral ganglion cells of mammals [54, 55]. The activation of Na, K-ATPase by GC could have positive effects on unbalanced intracellular and extracellular osmolarity, electrochemical gradients and neuronal activities, which are disturbed by noise-related cellular, functional cochlear damage and autoimmune inner ear disease [56, 57]. It is interesting that GC, despite their conventional effects at physiological concentrations, have various therapeutic application at higher doses, through different mechanisms: immunosuppressive effects (inhibition of the activation of T lymphocytes), anti-inflammatory (through blockade of proinflammatory mediators), antiproliferative effect (through suppression of collagen synthesis and fibroblast formation) and immunosuppressive one (through the inhibition of the activation of T lymphocytes) [58]. The use of GC is justified by the fact that steroids are able to reduce inflammation and edema in the inner ear, typical in the idiopathic, SSNHL. Despite the numerous clinical trials, the value of steroids in the treatment of SSNHL remains unclear, but the administration of high-doses of corticosteroids is recommended and primary performed in clinical routine practice [59, 60].

PHARMACOLOGICAL MANAGEMENT: ORAL AND INTRATYMPANIC CORTICOSTEROID THERAPY

Oral/systemic corticosteroid administration is the most frequent primary pharmacological treatment and is widely considered most efficacious for its ability to reduce the inflammation and the edema in the inner ear [10]. Although, there aren't many data to support this recommendation, in fact, different studies showed that oral steroids administration, such as methylprednisolone or dexamethasone, administered over a period of 10 to 12 days, was able to induce a significant higher rates of improvement among patients [61]. The efficacy of systemic corticosteroid treatment seems directly related to the time between the onset of the disease and the start of the pharmacological treatment [62]. Studies taking into account the relationship between the duration of SSNHL before pharmacological therapy and outcomes have reported the greatest recovery of hearing when corticosteroids were given within the first one to two week after symptom onset, and little if any when initiated four weeks or longer after the onset of the symptoms [63-65].

Some clinical studies evaluated the effects of oral corticosteroids vs oral placebo for the treatment of SHHL [65]. Wilson et al., [61] showed that dexamethasone (0.75 mg twice daily to 4.5 mg twice daily) or metylprednisolone (4 mg/d to 16 mg three times daily) have the same anti-inflammatory effects. In particular, these clinical research showed that

corticosteroids was able to reduce the pure-tone average, measured at four and three months after the onset of SSNHL, thus bringing to a greater rate of recovery in patients treated with steroids than to placebo control group [61]. In contrast with these studies, randomized controlled studies conducted by Nostrati-Zerenoe and Cinamon have failed to demonstrate a beneficial effect of systemic steroids administration [66, 67]. In particular, Cinamon and colleagues have found that prednisone (1mg/kg daily) was not able to reduce the pure-tone average scores, speech frequency, high tone hearing levels, and discrimination scores at 6 days and 14 to 90 days (follow-up) after treatment.

These reports together with the side effects induced by corticosteroid administration (mood changes, elevated blood pressure and sugar levels, loss of appetite, weight gain, gastritis, sleep disorders and hyperglycemia) ensure that oral therapy is to be considered carefully, in particular in patients with other chronic diseases such as sleep disorders or diabetes mellitus.

In alternative of oral corticosteroids, some otolaryngologists recommend local corticosteroid therapy for SSNHL. This treatment is based on the local glucocorticoid injection, directly into the ear in order to reduce the risk of systemic side effects, typical of oral administration, allowing glucocorticoids to penetrate directly into the cochlea and achieve a high concentration there even when low doses are used [65-69]. This procedure consists in the administration of methylprednisolone, dexamethasone and prednisolone, drugs able to affect the immune suppression and the ion homeostasis [70], by intratympanic or as eardrops by means of ventilating tube or a 'wick' running from a ventilating tube to the round window membrane in the medial wall of the middle ears. In this way, corticosteroids are available in high concentrations in the target tissue, promoting a reduction of inflammation associated with labyrinthitis, an enhancement in cochlear blood flow and improving striavascularis functions.

During the last years, different researches have taken into account the use of intratympanic steroid as the primary treatment of idiopathic SSNHL. Two multicenter studies, conducted by Battaglia et al., [71, 72], have found that association between intratympanic dexamethasone (12 and 10 mg/ml) and high-dose oral prednisone resulted in a significant improvement of hearing, respect to the treatment with oral prednisone alone.

Two reports about the efficacy of local corticosteroid therapy showed that the association between 5 mg/ml dexamethasone with i.v steroid are able to induce an improvement of the hearing functions in patients affected by SSNHL [73, 74]. These studies, taking together, demonstrated that a combined therapy was more effective for SSNHL in achieving hearing gain than corticosteroids alone. Furthermore, when administered alone as primary therapy, intratympanic steroids have been shown to be as effective as systemic steroids. An elegant research conducted by Rauche and colleagues [75] showed that methylprednisolone (40 mg/ml) was able to improve the pure tone average when compared to oral corticosteroid treatment, rejecting the hypothesis of the inferiority of intratympanic administration with respect oral prednisolone. In conclusion intratympanic injection may be an alternative method, particularly for patients who have high risks of complications, due to the oral therapy, although the evidences supporting this strategy is even more limited.

PHARMACOLOGICAL MANAGEMENT: VASODILATORS AGENTS

The speculation about the pathogenesis of the SSNHL lead to the investigation of several other pharmacological agents to treat this disorder.

The hypothesis about the involvement of microvascular dysfunction in the cochlea as major cause of idiopathic SSNHL, different vasodilators and blood thinners are widely suggested as agents able to increase the caliber and blood flow in vessels, in order to rule out the problem.

A research by Zhuo and colleague [76] pointed out the attention on the role played by the Prostaglandine E1 (PGE1), a prostanoid with vasodilator properties, in the treatment of SSNHL. In this study the author showed that PGE1 might be beneficial, probably due to its ability to increase cardiac output, improving cochlear blood flow [77]. Although this study appeared to be favorable to the use of PGE1, a prospective, double blind, randomized controlled study, showed that either PGE1 or placebo, used in addition to a steroid in each experimental condition, do not have a beneficial effect on the treatment of idiopathic SSNHL [78].

Moreover, in order to enhance the microcirculation, other compounds with cerebral vasodilator activity have been studied. A prospective, single blind, randomized controlled study investigated the efficacy of carbogen, a gaseous mixture of 5% carbon dioxide and 95% oxygen, known for its ability to increasing the partial oxygen pressure of perilymphatic fluids, on idiopathic SSNHL. This study showed that carbogen treatment was able to increase the hearing ability with respect to control group [79].

CONCLUSION

Despite specialists are unanimous about the identification of the typical symptoms of the SSNHL, the research and the evaluation of the main causes that trigger this auditory disability are characterized by contrasting opinions. Nevertheless, different pharmacological treatment are known and have been engaged to ameliorate the idiopathic SSNHL. Treatment regimens have included minerals, essential minerals, antimicrobials, vitamin, antiviral and diuretics agents, in addition to herbal preparations. Although initially promising results are found in different case reports and small trials, surprisingly there is a little persuasive evidence that supports the efficacy of these pharmacological agents in alleviating the symptomatic conditions that afflict patients with SSNHL. Among all the different therapies, corticosteroids appear the prominent current standard care to improve or restore hearing.

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Chapter 67

MANAGEMENT OF SENSORINEURAL HEARING LOSS WITH HEARING AIDS

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ABSTRACT

Sensorineural hearing loss (SNHL) is a disease affecting the hair cells of the cochlea. Congenital SNHL is mainly due to genetic mutations, infectious agents and hypoxia, whereas acquired forms are mostly caused by aging (presbycusis), noise exposure and ototoxic drugs, although genetic mutations and infections by neurotropic viral agents are recognized etiologic factors in this category, as well. SHL can also be classified according to laterality into bilateral and unilateral, and according to the degree of hearing loss into mild, moderate, severe and profound.

Modern hearing aids are digital amplifiers receiving sound energy at their microphones, converting it into digital information by means of their processor, and transforming it back into an analogue signal for the receiver. Traditionally they are divided into behind-the-ear and in-the-ear hearing aids, based on the position.

Hearing aids represent an effective treatment of SHL when there is a cochlear reserve, i.e., in cases where residual hair cells are in a sufficient number to be appropriately stimulated. Especially in children affected by prelingual, profound deafness, they can still be used in to get the subject trained to acoustic stimulation before he/she receives cochlear implantation.

Whereas hearing aids are the standard treatment of mild, moderate and severe forms of bilateral SNHL, their indication in patients with unilateral SNHL is much debated.

Keywords: hearing loss, hearing aids

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INTRODUCTION

Hearing loss is the most frequent sensory deficit in human populations, affecting more than 250 million people in the world [1]. Its causes may be congenital, such as for example the 35delG mutation of the connexin 26 gene [2] and intrauterine cytomegalovirus infection, or acquired, such as hearing loss determined by noise exposure [3-8]. Consequences of hearing impairment include inability to interpret speech sounds, often producing a reduced ability to communicate, delay in language acquisition, economic and educational disadvantage, social isolation and stigmatization.

Hearing loss is the most prevalent sensory deficit, and represents a major public health issue with substantial economical and societal costs. Untreated, child hearing loss leads to significant language delay and impaired auditory-verbal communication, while in adults it results in communication difficulties that can lead to social isolation and withdrawal, depression and reduced quality of life [9, 10]. Hearing loss is also associated with an increased risk of dementia, and this is true especially for older adults [11, 12].

So far, it has not been possible to resolve the causes of sensorineural hearing loss, which can only be aided by means of sound amplification. Gene therapy, consisting of direct administration of genes regenerating the sensory epithelium, or stem cells differentiating into mature cells of the organ of Corti have no clinical application at the moment [13]. Although causal therapy of sensorineural hearing loss is not to be expected for the near future, there are currently several possibilities of hearing aid amplification that can compensate it.

Shared indications to hearing aid application include the following conditions [14]:

- surgical hearing improvement is not possible
- pure tone audiometric hearing loss in the better ear ≥ 30 dB in at least one of the test frequencies in the 500-4000 Hz range
- speech recognition in the better ear (tested with headphones at 65 dB) $\leq 80\%$
- sufficient cooperation by the patient

FUNCTIONAL PRINCIPLES AND ESSENTIAL COMPONENTS OF HEARING AIDS

Modern hearing aids rely on a completely digital signal processing. The sound is first received by a microphone, which converts it into an electric signal. Then, the electric signal is transformed into a discreet pulse sequence by an analogue-to-digital transducer. Finally, the digital sound is again transduced into an electric sound, which is picked up by the receiver that converts it into sound waves for the patient's ear.

The microphone includes a diaphragm that is set into vibration by the pressure variation of sound waves that enter the opening of the microphone itself. The motion of the diaphragm transduces the acoustical energy to electrical energy.

The Digital Sound Processor (DSP) represents the sound by analyzing it at discrete intervals and converting it to a series of numbers according to specific algorithms. Typically, the sampling rate of modern hearing aids is around 20 kHz. Therefore, a theoretical limit of

10 kHz is determined for further signal representation and processing. After digital conversion, the discrete signals are separated in the hearing device into several frequency bands, corresponding to 4–20 channels. Each channel performs the signal processing, including frequency-specific amplification, independent of other channels. The number of channels, which sets the number of independently adjustable frequency ranges. This number plays a central role in sensorineural hearing losses where only a part of the frequency range is affected, such as high-frequency hearing loss. Since typically only 10 different frequency values are tested in tone audiometry, the number of channels is no longer a challenge from a technical point of view.

Finally, the separately processed signals are merged, amplified, converted back to analogue signals (digital-to-analogue transduction) that are delivered to the ear via a receiver.

The receiver is also a transducer, transforming electrical signals into acoustic sound waves. Like the microphone, it has a diaphragm that is set into vibration, but its movement creates the sound waves that travel through the tubing connecting the receiver to the outside.

CLASSIFICATION OF HEARING AIDS

According to manner of placement, hearing aids can be classified into:

- *Custom-molded hearing aids*, made from an impression of the user's ear. The electronics of these aids are housed in hard plastic, although soft materials are sometimes used for the portion located in the auditory canal. Although they offer the potential for better quality control, they generally suffer from size and shape limitations that adversely impact cosmetics and the functional integration of the hearing aid and earmold.
- *Completely-in-the-canal (CIC)* hearing aids, the most cosmetically appealing and smallest contemporary hearing aid styles, they often have their electronics completely within the cartilaginous segment of the external auditory canal, although some extend into the bony portion of the canal, terminating close to the tympanic membrane. Despite gain and output of these hearing aids are limited because of small transducers, they allow the patient to benefit from improved cosmetics, greater overall sound pressure level especially for the high frequencies, reduced occlusion effect and feedback and normal telephone use.
- *In-the-canal (ITC)* hearing aids, sized between the CIC and the in-the-ear (ITE) hearing aid, they fit within the concha and the cartilaginous portion of the external auditory canal, with the microphone opening located at the outer portion of the concha. Because of vents, "feedback control" trimmers may be needed, which attenuate the high frequencies. Owing to deeper insertion than ITE aids, they often require lower gains and provide a better high-frequency response, while size limits the number or dimension of circuits and trimmer controls, together with use of the large vents that could suppress the occlusion effect. For users, telephone use is much easier with this hearing aid type than with a larger ITE device thanks to reduced

feedback, more favorable microphone locations and larger air volume under the telephone receiver.

- *In-the-ear (ITE)* hearing aids include “full concha,” “low profile” and “half concha” instruments. Full concha ITE aids are the most common, allowing the entire concha volume to be filled with electronics and therefore enabling the implementation of complex circuit designs, venting and performance control.
- *Behind the Ear (BTE)*: the hearing device is above the auricle and the processed sound is conducted into the auditory canal either electrically or via a sound tube. BTE hearing aids can be divided into the traditional ones, with a receiver within the case of the hearing aid, and those with a receiver removed from the case and instead located at the end of the tubing and placed inside the auditory canal (receiver-in-the-canal or RIC). BTE aids can be worn in an “open” configuration, where the coupling consists of a tube to the ear and the ear domes do not completely occlude the ear. Open fitting is particularly good for subjects with normal hearing in the low frequencies and hearing loss in the high frequencies, because the low-frequency sound can exit the ear canal as it does for normal-hearing listeners.

TYPES OF AMPLIFICATION

The most common ways to provide amplification in a hearing aid are linear and non-linear amplification. In the context of linear amplification, all input levels are amplified to the same extent until the hearing aid reaches output sound pressure level 90. This way, a sound entering the hearing aid is increased of a constant decibel value. This type of amplification is suitable for low-grade sensory hearing losses or conductive hearing losses. In cases of higher-grade hearing losses with defined recruitment a lower amplification has to be set for higher input levels in order to consider the discomfort limit. This goal is achieved by means of amplitude compression. In amplitude compression systems, a linear amplification is typically applied up to a certain input level, whereas it is reduced for higher levels. The non-linearity can be described by the knee point, i.e., the point where the output curve deviates from linear, and the compression ratio, i.e., the degree of such a deviation. There are several compression variants that function in a similar way.

Another type of special, non-linear of amplification is achieved by frequency lowering or reduction [15], a function that changes the spectral representation of sound signals and can be obtained both as frequency transposition and as frequency compression. The rationale behind frequency reduction is that most sensorineural hearing losses are characterized by a descending auditory threshold for high-frequencies, for which an amplification is neither useful nor possible. By taking high-frequency input signals and presenting these sounds to lower-frequency regions, the hearing aid allows the patient to hear otherwise inaudible and not amplifiable sounds. Frequency reduction is possible either via frequency transposition, whereby the signal is lowered by a fixed frequency value with no alteration of the overall bandwidth, or via frequency compression, whereby both frequency and bandwidth are reduced by a preset ratio. These procedures are associated with unavoidable signal distortions. In many cases, however, a better hearing perception can be achieved after some months of

acclimatization. It is important to remind that frequency reduction does not so much lead primarily to a better speech understanding than mainly improve sound impression [16]. Since frequency reduction algorithms are initially disturbing, the possibilities to implement them in commercially available hearing aids are rather limited.

Up to now, there is no possibility to identify particular subjects who might benefit from frequency reduction. In contrast to earlier analogue aids, not only the hardware but also the quality of technical components in digital hearing devices is essential. The function of a hearing aid is determined by the signal processing defined in the software. Thus, there are today technically identical hearing aids that are only different regarding their technical features (and price). The software determines for example the feedback suppression, wind noise suppression, directional microphones etc.

FITTING OF HEARING AIDS

The fitting of a hearing aid is a process of several weeks and months in which the most suitable hearing aid is identified and the optimal settings for daily life are established. First, the audiological profile is determined by measuring the severity and the type of hearing loss and the individual needs are assessed. It is clarified which hearing conditions appear frequently and are especially relevant. Patient needs or request to be taken into account at this stage are: speech understanding in quiet compared to in noise, telephone use, frequent lecture situations (e.g., school children or students), or specific requests for directionality (e.g., taxi drivers), or special requirements regarding dirt and water repellency (e.g., pool attendants). Additional settings must also be considered: are highly different settings constellations necessary? Does switching have to be automatized or at the touch of a button? Those and other similar questions lead to a selection of the possible hearing aid. The initial setting of the hearing aid is generally performed by means of a software according to audiometric parameters such as hearing (air and bone conduction) and discomfort thresholds, even loudness scaling if needed. Because of the approximation of measurements, most hearing aid fittings are performed only based on tone audiograms and the discomfort thresholds are directly estimated by the fitting programs.

The objective of compensation in cases of sensory hearing losses is never the complete amplification of an existing hearing loss, whereas the target amplification is rather at half of the hearing loss dynamic range. Most fitting formulas such as the National Acoustics Laboratories of Australia (NAL) [17], the Prescription of Gain and Output (POGO) [18] generally correct the values, adjusting them downwards for higher frequencies and upwards for lower frequencies. Other procedures such as the Desired Sensation Level (DSL) [19] try to restore the loudness sensation via the dynamic range and thus require the measurement of individual loudness scaling over several frequencies.

In the practice, hearing aid fitting is completely performed by the software provided by the hearing aid manufacturer. Based on the audiometric data, the prescription is calculated and the hearing aid is programmed. Additional information such as having to do with an inexperienced or with an experienced hearing aid user lead to further automatic adjustments. Furthermore, other modifications of the hearing aid settings can be performed after testing the

device in daily routine. Finally, fine tuning must take into account the hearing environment and include algorithms to optimize sound quality.

TECHNOLOGICAL ADVANCEMENTS AND FUTURE DEVELOPMENTS

Modern hearing aids are miniaturized high-power computers that have to function with little energy for a possibly long duration. While formerly hearing aids were limited by the components (microphone, amplifier, receiver), the quality of a modern hearing device is rather defined by the immanent software. Even if there are permanent improvements of the hearing aid technology, exaggerated advertising measures often lead to disappointments owing to the fact that the effectiveness of the single improvements is not always noticeable. Nonetheless, several improvements could be observed over the past years.

Directional microphones are useful when the speech signal comes from the front and the background noise from other directions. Nowadays, directional microphones cannot only be implemented as a fixed part but they can also be digitally added. Adaptive directional microphones only switch on when a speech signal is recognized as coming from the front. This is possible due to the evaluation of the time delay of the sound input at two different microphones.

Wind noise elimination: the wind reaching a normal hearing ear is mostly well eliminated and only rarely leads to noticeable hearing deterioration. Since most of the hearing aid microphones are located above the auricle, this natural protection is missing. Furthermore, most microphones have a directional effect set to the front. Thus, also low wind velocities lead to significant deterioration of the signal quality. In the past, this fact led to dissatisfaction in nearly half the hearing aid users [20]. Several algorithms for wind noise reduction were thus developed, with the aim to increase the wearing comfort and also to improve speech understanding in challenging acoustical environments.

Binaural coupling: coupling two hearing aids of the same user became possible after the development of an appropriate wireless protocol. Initially, binaural coupling was limited to the (wireless) transmission of parameter settings of one hearing aid to another. In this context, for example, the change of loudness in one hearing aid was also effective in the contralateral one. Later, this feature was extended by real time transmission of audiodata. This way, a very important directional effect of the microphones can be achieved. Additionally, the hearing aid can recognize on which side the speech signal is presented and amplify it. During phone calls, such devices can transmit the telephone signal to both ears. It is highly efficient to use binaural coupling also to suppress wind noise when they only occur in one ear.

HEARING AIDS FOR UNILATERAL HEARING LOSS IN CHILDREN

Although a hearing aid may be a useful intervention option for children with unilateral hearing loss (UHL) who have usable residual hearing in the impaired ear, clinicians do not appear to be making this recommendation consistently. Only 26% of children with UHL received an initial recommendation for amplification [21], whereas across studies 48% of children with UHL received a conventional hearing aid [22, 23]. A parental survey indicates

similar findings: 42% of families of children with UHL were told that hearing aids would not help, although only 8% of the children had no residual hearing [24]. However, evidence indicates that a conventional hearing aid does provide benefits: 20 parents of children with mild to moderate UHL surveyed via a questionnaire reported improved hearing and better performance in academic and social situations with a hearing aid and many parents indicated that they wished their child had received a hearing aid sooner [25]. Children with UHL who used a hearing aid have also reported greater ease of listening in quiet and noise [22]. Even with no measurable change in speech perception, subjective reports from parents, teachers, and children showed significant aided benefits at home, school and quality of life [26]. Younger children with mild to severe UHL have also shown significantly improved localization, although children who were fit later showed bilateral interference [27]. Yet only about 26% of children with UHL use their hearing aid full-time; compared to 72% of children with a moderate bilateral hearing loss. This reduced compliance in children with UHL may be because they are often fit with hearing aids later than children with bilateral hearing loss, and wearing compliance is typically poorer when children are fitted later [28]. One limitation in fitting a hearing aid to children with UHL concerns the prescriptive method used: there is no evidence to date to indicate whether children with UHL prefer the gain from prescriptive methods designed for bilateral hearing loss [29]. A possible solution to this problem has been suggested [30], which is to use a technique to achieve binaural fusion in individuals with asymmetric hearing losses [31-32]. However, this method requires patient participation and therefore is not useful in fitting infants and young children with UHL.

Overall, the evidence indicates that children with UHL who have usable residual hearing in the affected ear can receive benefits from conventional digital amplification including greater ease of listening, better performance in academic and social situations, and improved localization if fitted early.

HEARING AIDS FOR UNILATERAL HEARING LOSS IN ADULTS

Adults with UHL also have positive outcomes with conventional hearing aid use. Of 119 adults with UHL who were fit with a conventional hearing aid, 68% continued use 6 months post-fitting and the primary predictors for successful hearing aid use were social/work activities and digital signal processing [33], suggesting that although individual demands on communication may affect use, advanced technology devices may be more appropriate for individuals with UHL.

In adults, unilateral hearing loss is often acquired suddenly and accompanied by tinnitus [34-36]. Positive outcomes of hearing aid use in the adult population are reported as well. Of 119 adults with UHL who were fit with a conventional hearing aid, 68% continued use 6 months post-fitting and the primary predictors for successful hearing aid use were social/work activities and digital signal processing [37], suggesting that although individual demands on communication may affect use, advanced technology devices may be more appropriate for individuals with UHL.

Unfortunately, there are only few studies that examine the effectiveness of hearing aids on tinnitus alone. With hearing aids, many patients experience effective relief of their tinnitus, but studies on hearing aids as solitary therapy do not exist because they are always embedded

in an audio-therapeutic concept. Nonetheless, hearing aids are essential in the tinnitus therapy because they nearly always include and compensate the existing hearing loss. In a retrospective tinnitus analysis [38-39], 58 tinnitus patients with hearing loss were followed-up; 29 used hearing aids, 29 did not – both groups had nearly identical audiograms, the same duration of tinnitus, and the same age on the average. Only in the group of hearing aid users, a significant improvement of the tinnitus could be achieved based on the Tinnitus Handicap Questionnaire.

Another work reported about 74 tinnitus patients who received hearing aids with a linear frequency transposition [40-41]. Those hearing aids are especially active in the high frequencies and very suitable for patients with a steep drop of the hearing curve. In 60 patients, the tinnitus could be permanently eliminated. In this study, patients whose hearing loss was related to noise exposure had permanent tinnitus suppression a few days after starting hearing aid use. A review study from the Netherlands reviewed 10 articles, showing improvement 25–72% of the patients and complete tinnitus suppression in 8–45% of the patients. Up to 25%, however, even mentioned deterioration, new additional tinnitus developed in up to 10% [41].

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Chapter 68

COCHLEAR IMPLANT OF SNHL PATIENTS

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ABSTRACT

Sensorineural hearing loss (SNHL) is the most common type of hearing loss. The key to the optimal management of congenital SHL is early diagnosis (achieved through the diffusion of Newborn Hearing Screening programs) and early intervention. Treatment for SNHL varies, depending on the severity of the loss itself. Although hearing aids can help most people with mild to moderate SNHL, they are often not sufficient for spoken language development in more severe hearing losses, where cochlear implants represent the gold standard of the treatment. A cochlear implant is a surgically implanted electronic device. Unlike hearing aids, which simply amplify sound, cochlear implants pick up sound and digitize it, convert that digitized sound into electrical signals, and transmit those signals to electrodes embedded in the cochlea. The electrodes electrically stimulate the cochlear nerve, causing it to send signals to the brain. There are several systems available, but generally they have similar external (speech processor, transmitter, microphones) and internal (receiver-stimulator, electrode array) components. The ideal timing for cochlear implantation is between 12 and 18 months of age, and it can be done simultaneously or sequentially. Results vary from person to person. The main factors that can affect the outcomes of cochlear implantation include the age when hearing was lost, the length of time between hearing loss and cochlear implantation (hearing deprivation), and the timely inclusion in an appropriate speech therapy rehabilitation program. Research indicates that children who undergo bilateral (either early sequential or simultaneous) cochlear implant surgery at young age develop better hearing and speech than similar children with hearing aids or who received one cochlear implant or two cochlear implants after longer hearing deprivation. The benefit of cochlear implantation in children with single sided deafness is currently under investigation.

INTRODUCTION

Sensorineural hearing loss (SNHL) affects 1 to 3 of every 1000 children born in developed countries [1, 2]; the rate is probably higher in the developing world [3]. In most cases, the hearing loss is nonsyndromic (i.e., it is not associated with other congenital features) and the child is otherwise healthy. The lack of auditory input during the child's development has a minimal effect on his or her motor and social development during infancy. Thus, if infant hearing screening is not performed, the deafness is often unnoticed during this period, resulting in a late diagnosis (at ≥ 1 year of age) [4]. The deaf child receives little or no access to environmental sounds and speech; this lack of access arrests or disrupts normal auditory development [5-9]. As the child grows older, auditory deprivation results in cortical reorganization, including an expansion of visually driven inputs into the secondary areas of the auditory cortex. The duration of deafness before diagnosis and intervention is negatively correlated with the child's ability to perceive and use spoken language after being fitted for an auditory prosthesis [10]. Universal newborn hearing screening, which is now available in most countries, has markedly improved the early diagnosis of sensorineural hearing loss.

Effects of Hearing Loss

It is well documented that childhood deafness can have a severe impact on speech and language development, which can result its emotional, social, educational, and vocational disruption as the child matures [11]. In our society, oral language is the primary means through which socialization and learning occur. Development of speech and language occurs rapidly in the first few years of life, primarily through normal family interaction. If the communication interaction between child and family is disrupted during these early critical years, serious delays are likely to occur. If the deprivation goes on for too long, the child may never make up the lost learning, even with extensive rehabilitation. Supporting this claim, the average reading level of deaf 18 year old persons is just below the third grade level [12]. Adults who have been deaf since childhood tend to be undereducated and earn less money, compared with their hearing peers [13]. Severe to profound hearing loss has the potential to adversely affect many aspects of development, including social, cognitive, and academic abilities, primarily because of language delay [14]. In the long term, deficits in these areas can limit vocational and economic potential. Unlike many clinical conditions, the management and treatment of SNHL largely involves the social welfare and educational systems rather than the medical care system. For a child with congenital severe to profound SNHL, the total lifetime cost of hearing loss exceeds US\$1000000. Special education costs amount to over half of this total, and medical expenses and the purchase of assistive devices add another US\$100000 [15].

Cochlear implants are electronic devices which have been approved as method of treating profound, bilateral, sensorineural hearing loss for persons since the mid-1980s [16]. Although the original cochlear implants were single channel devices, there are now several commercially available, multichannel cochlear implant systems. Additionally, over the course of the last two decades, technological developments in cochlear implant design have yielded substantial gains in spoken word recognition for the average multichannel cochlear implant

user. Along with advances in engineering and speech processor design have come changes in the criteria for cochlear implant candidacy. For example, initially only adults with postlingual profound deafness were considered suitable candidates for cochlear implantation; now, audiometric thresholds are no longer a primary determinant of cochlear implant candidacy for postlingually deafened adults. Similarly, congenitally deaf children initially were not considered suitable candidates for multichannel cochlear implantation. When implantation of children was approved by the FDA it was limited to children 2 years of age and up; now, the FDA has approved the use of multichannel cochlear implants in prelingually deafened children as young as 12 months of age, and many children younger than 12 months of age have been implanted off protocol.

CANDIDACY CRITERIA FOR COCHLEAR IMPLANTATION

FDA Guidelines

The FDA has approved cochlear implants for children with severe-to-profound bilateral sensorineural hearing loss (hearing threshold, ≥ 90 dB in the better ear) who are at least 1 year of age and who have not benefited from an adequate trial (typically 4 to 6 months) of hearing-aid amplification. A similar position was taken in 2000 in a statement of the Joint Committee on Infant Hearing [17], which noted that “cochlear implants may be an option for certain children age 12 months and older with profound hearing loss who show limited benefit from conventional amplification.” Currently, clinical practice in recent years has expanded beyond these criteria. Guidelines for cochlear implant candidacy have changed substantially over time. For instance, in the 1980's cochlear implants were recommended for post-linguistically deafened adults with hearing losses greater than 100 dB and no discernable communication benefit from a hearing aid. By the year 2000, FDA approval had extended the implantable age down to 12 months and broadened the general hearing criteria. Current guidelines permit cochlear implantation in persons age 2 years and older with severe-to-profound deafness (i.e., pure tone average thresholds of 70 dB HL or greater), and in children 12 to 23 months of age with profound deafness (i.e., pure tone average thresholds of 90 dB HL or greater.) Whenever possible, outcomes from word and sentence recognition testing are also used to determine candidacy. Current guidelines permit implantation in adults with open-set sentence recognition scores of approximately 50% to 60% words correct. As cochlear implant devices continue to improve, the criteria regarding the degree of hearing loss and the performance with a hearing aid that warrants consideration of a cochlear implant also will continue to evolve.

Medical Evaluation

The medical evaluation examines the status of the patient's overall health, the history and etiology of the patient's hearing loss, and the physical condition of the ear and cochlea. The general health of the patient impacts his fitness for general anesthesia and surgery, and his ability to complete the necessary post-operative programming of the device. Although general

health status is rarely a contraindication for implantation, it may affect the timing and preparation for implantation.

Etiology

At present, the etiology and history of a patient's hearing loss cannot accurately predict a patient's performance with the cochlear implant. However, some general relationships have been reported that can moderate the patient's expectations. For example, persons with deafness subsequent to meningitis commonly develop cochlear ossification that can impede the insertion of the electrode array. The degree of cochlear ossification may affect the prognosis for implant performance and increase the possibility of facial nerve stimulation. Individuals with partial insertion of the electrode array perform similarly to those with complete insertion as long as a sufficient number of electrodes can be activated to program the device [18-20]. Individuals with complete cochlear ossification who require a "drill-out" of the bone to provide a space to lay the electrode do not achieve as high a level of auditory perception with their implant [20]. They also are more prone to complications of facial nerve stimulation and pain associated with implant activation [21]. The possibility of less than average performance and a higher incidence of stimulation complications in cases of complete ossification needs to be discussed frankly with a patient and can sometimes affect the patient's decision to proceed with implantation.

History of Hearing Loss

Postlingually deafened adults with a history of progressive hearing loss and a shorter duration of deafness tend to achieve higher speech perception scores than those who have been deaf for a long period of time prior to implantation [22-25]. Adults with prelingual hearing loss generally are not considered good candidates for cochlear implantation, especially if they do not use oral/aural communication [26]. Similar relationships exist between the history of hearing loss in children and performance with an implant, although they are moderated by a child's development. The origins of deafness in children are manifold. The difference must be made between congenital and acquired causes as well as the time of deafness (pre-, peri-, or postlingual). If the onset is observed before language acquisition, the term of pre-lingual deafness is applied, after final language acquisition (around the 10th year of life) it is called post-lingual deafness. If hearing loss is detected during the phase of language acquisition, it is the case of a peri-lingual deafness. The impact of hearing loss on the language development is well-known [27]. It is crucial for the therapeutic success of a cochlea implant to possibly early detect, diagnose, and treat hearing loss in order to keep the consequences of the auditory deprivation for hearing and language development as well as the general mental development on a low level [28]. Hereby, also the development of a binaural hearing system as base of directional hearing and speech understanding in noise must be mentioned. In cases of congenital deafness, the newborn hearing screening is essential for early detection. In contrast to adults, both pre- and postlingually deafened children are candidates for cochlear implantation as long as they receive little or no benefit from conventional amplification. In some instances, better hearing

sensitivity before implantation and the use of spoken language in a child's communication and educational setting have been associated with better speech perception [29, 30].

Radiological Examination

High-resolution imaging (Computerized Tomography, CT and Magnetic Resonance Imaging, MRI) is used to estimate the patency of the cochlea and to identify any abnormal anatomical variations that may affect insertion of the electrode. Although imaging may miss some obstructions preventing electrode insertion, this is rare [31, 32]. Some obstructions can be anticipated on the basis of the clinical history of hearing loss. As noted above, clinical histories of otosclerosis or meningitis commonly are associated with cochlear ossification.

Genetic Diagnostics

One relevant pillar of the etiological clarification is the genetic diagnosis. About 50–60% of pediatric hearing impairment are due to a genetic predisposition. They are classified into non-syndromic and syndromic types of hearing loss, i.e., generally the hearing loss is a symptom in the context of a syndrome. Currently, more than 200 so-called deafness genes are known [33]. The most frequent expression is the mutation on the gene locus GJB2 that leads to a disorder of the connexin molecule (Connexin 26), a gap junction protein. The consequences are disorders of the ionic homeostasis of the hair cells that are irreversibly damaged by a potassium intoxication. The difference is made between autosomal recessive, autosomal dominant, X-linked, and mitochondrial, genetically caused hearing losses. Autosomal recessive types often reveal deafness already at birth and are entitled DFNB (e.g., DFNB1 with connexin 26 disorders). Autosomal dominant types often have a postnatal onset and are progressive (DFNA) [33]. X-linked hearing losses are located on the X chromosome and only appear in males (DFN). Mitochondrial hereditary hearing impairment is passed on by maternal genes.

Audiologic Evaluation

The purpose of the audiological evaluation is to quantify the candidate's preoperative hearing, communicative status, and use of prosthetic devices. The results are useful in determining candidacy by comparing the current communicative status to the expected outcome of using a cochlear implant. Results also are important as pre-outcome measures to quantify the benefit of the cochlear implant after implantation. To this end, the audiologic evaluation comprises of a pure-tone audiogram including air and bone-conducted thresholds, tests of speech perception such as word and sentence recognition, an evaluation of current amplification, and, if appropriate, a trial use of amplification. Speech perception tests are most decisive in determining the appropriateness of cochlear implantation. Candidates who demonstrate open-set word or sentence recognition performance that is below the average scores seen for cochlear implant recipients should be considered for implantation. Indications in children – Cochlear implantation in children should be performed immediately after

indication. Bilateral implantation should be performed in cases of bilateral profound deafness, if possible simultaneously or otherwise as sequential implantation with a short time interval in order to use the sensitive phase for the development of binaural hearing [34, 35]. Hearing aid fitting beside unilateral cochlear implantation is indicated in cases of asymmetric hearing with unilateral sensory hearing loss and useable hearing ability in the contralateral ear. Narrow controls of the residual hearing as well as the hearing success in this ear must be performed so that progressive hearing loss or development failure of bilateral hearing are detected in time and the point of then necessary sequential cochlear implantation of the second ear may be correctly chosen [28-36]. If maturation is delayed, as it may be expected in cases of increased hearing thresholds and prolonged inter-peak latencies in brainstem audiometry, control examinations in narrow intervals and probatory hearing aid fitting seems to be appropriate.

Often hearing improvement is observed due to maturation of the peripheral auditory system and the central hearing pathway so that a repetition of the examination of the residual hearing after some weeks or months is indicated. If no significant improvement of hearing is observed, cochlear implantation should be performed in the second year of life at the latest. In this context, the so-called perisynaptic audiopathy must be mentioned summarizing disorders of the inner hair cells, the synapsis to the afferent nerve fibers as well as true auditory neuropathy with damage of the afferent neuron (auditory neuropathy spectrum disorder). This term encompasses different pathophysiological disorders of stimulus transmission and stimulus forwarding in the peripheral auditory system. Only in the context of true auditory neuropathy a relative contraindication for a cochlear implant system exists. In cases of particular urgency such as for example threatening cochlear obliteration by labyrinthitis and meningitis require immediate, early implantation.

Performance Measures in Children

The audiological evaluation of young children for cochlear implantation assesses the ear's sensitivity to sound, and, if possible, includes measures of auditory perception. As the age of implantation decreases, visual reinforcement audiometry and auditory evoked response audiometry are the primary methods of measuring hearing sensitivity. Speech/auditory perception testing depends upon the age and linguistic ability of the child. Again, a large number of pediatric perception tests exist which vary from open-set word and sentence recognition, to closed-set measures of prosodic features, word identification, and speech feature identification [37]. For the youngest children, parental reporting scales of auditory listening behavior, such as the Infant-Toddler Meaningful Auditory Integration Scale [38] frequently have been used to assess auditory skill development. For older children, open-set word and sentence tests are employed to determine candidacy. Less difficult tests that include closed-set measures of performance, such as the Early Speech Perception Test [39] can be included if open-set word recognition is not possible. By using tests appropriate for the age and language level of the child, one can scale the child's ability along a continuum and chart a child's progress over time. As the age of implantation decreases, candidacy criteria are generally determined by a lack of progress noted on parental scales of auditory skill development over a given period of time (such as three to six months). In very young children, candidacy also may be determined by the child's progress in developing spoken language with amplification, based on studies of spoken language acquisition in children with

cochlear implants versus children with different severity of hearing losses and hearing aids [40, 41].

Psychological/Rehabilitation Evaluation

An important aspect of cochlear implant candidacy that is much harder to define than the audiological or medical evaluation is the assessment of whether the candidate's overall life situation is one that will integrate and promote the use of a cochlear implant. The anticipation of cochlear implant surgery and the hope for a positive outcome introduces stress into the lives of the candidate and his or her family. Evaluation of a patient's family's expectations for life after implantation can be beneficial in tempering unrealistic expectations and anticipating alternative pathways if the postimplant performance is not as expected. In children, the psychosocial evaluation is more extensive and includes developmental and educational evaluations as well as family assessments. In the pediatric population, the choice of a cochlear implant is usually associated with the choice of spoken language as the primary communication mode of the deaf child and family. Establishing a plan of rehabilitation and education before implantation makes the integration of the implant smoother and reduces the likelihood that progress will be hindered by poor follow-through or gaps in rehabilitative services.

Patient Counseling and Expectations

Candidates for cochlear implantation come for evaluation with all levels of knowledge about cochlear implants and need to be informed of the potential risks and benefits of cochlear implantation and the impact it may have on their life. The surgical procedure and its risks should be described along with a physical description and, preferably demonstration, of the internal and external portions of the device. The various cochlear implant systems available at the center also should be shown and described to the candidate. The post-surgical programming commitment should be described and planned. In addition, potential cochlear implant candidates need to be aware of what day-to-day living with the device entails. This is best done by contacting other cochlear implant wearers and their families. The most important, yet sometimes difficult, aspect of patient counseling is generating realistic expectations regarding performance outcome with the implant. Almost all candidates (or their families) seek the implant because they want to improve their ability to hear and understand speech. Although the mean and range of performance with implants can be described, most people will naturally hope for the best of outcomes. Redundantly reviewing the range of performance, including the bottom of the range, during the course of the candidacy evaluation and discussing post-implant plans in case performance with an implant is poorer than anticipated can assist those recipients who obtain minimal postimplant benefit.

THE CI TEAM

Minimally, the role of a cochlear implant team is to determine candidacy for cochlear implantation, to help prospective recipients make informed decisions about cochlear implant surgery and device options, to provide necessary medical care, to carry out the surgical implantation, and to provide postimplant device setting and monitoring. Aural rehabilitation specialists, speech-language pathologists and educators play an important role in the preimplant evaluation and/or postimplant management of children with cochlear implants. Prelingually deafened children must learn to use the sound provided by an implant to organize and access spoken language and to produce speech that can be understood by others. Aural rehabilitation specialists and speech-language pathologists are members of some cochlear implant teams. Other teams may not have these professionals on staff; in that case, aural rehabilitation and speech-language pathology may be provided by private therapists or by school personnel. Because many children with cochlear implants require special classroom placement and educational support services, at least during the early years of cochlear implant use, it is important for cochlear implant professionals to work closely with educators in developing and coordinating appropriate intervention strategies. Larger cochlear implant teams may routinely include representatives of multiple disciplines; others may bring in additional specialists or refer to outside specialists as needed. Either way, it is important to have access to the disciplines required to provide quality health care. Hearing loss impacts not only communication and educational development, but also a child's emotional and social development. A number of cochlear implant programs have access to the expertise of psychologists or social workers who can assist families as needed. Close communication among the cochlear implant team and other professionals working with the child is essential for children to receive maximum benefit from a cochlear implant.

Otologist/Otosurgeon

The core personnel required to carry out these responsibilities include the surgeon (otologist/otolaryngologist) and the audiologist. Prior to implantation, the focus of care is determining medical and audiological suitability for cochlear implant surgery and managing any medical conditions that may prevent surgery. Following cochlear implant surgery and postimplant healing, the focus shifts from primarily medical management to primarily audiological management. Although the surgeon and audiologist have the principal roles in providing services to cochlear implant candidates and recipients, the needs of different populations may require the services and expertise of additional professionals, not all of whom need be involved with each potential candidate or implantee.

Aural Rehabilitation Specialists

The type of intervention provided by an aural rehabilitation specialist depends on his or her philosophy of communication development and on the needs of the child. A variety of philosophies exist concerning the appropriate communication methods for children with hearing impairment or deafness. One philosophy, oralism, promotes the development of

speaking and listening skills for communication. There are several different approaches within this philosophy. For example, some oral therapists use both lip-reading and listening as a means of learning to speak whereas others follow a more unisensory approach emphasizing listening alone without visual cues. An alternative philosophy promotes the use of sign language to develop communication skills, either alone or in conjunction with spoken language. Signing and speech used together is defined as total communication. In total communication, reception of language occurs through listening to speech and watching the signs. Expressive language is conveyed via speech and sign. The speech-language pathologist may be called upon to carry out evaluations of the child's spoken or signed communication abilities and to make recommendations for intervention. Some teams have speech-language pathologists who provide ongoing postimplant speech-language therapy to cochlear implant recipients.

Psychologist

The psychologist provides input related to the level of functioning and mental status of the child. The psychologist can also provide intervention when necessary or appropriate. For example, if family dynamics or behavioral problems present potential obstacles to success with a cochlear implant, the patient and family may be referred for counseling before and/or after cochlear implantation.

Neuropsychologist

Cochlear implant candidates may be referred for a neuropsychological evaluation if there is some concern about their ability to understand and actively participate in the preimplant and postimplant processes.

Educational Specialists

School personnel such as teachers of the deaf, itinerant teachers of the hearing impaired, and mainstream classroom teachers often work closely with the implant team during the evaluation and postimplant periods. They provide important information about how the child is functioning in his or her daily environment, and implement suggestions given by the team for maximizing communication. Sometimes a cochlear implant team includes an educator who assists in the planning of the educational placement and protocol. This individual can act as a formal liaison between the implant center and the school system.

Social Worker

The social worker can provide guidance and support to the child and the family in all areas, including financial planning. Social workers also may help to coordinate necessary appointments and services and provide counseling for families.

CI COMPONENTS

Cochlear implants are electrical prostheses that trigger auditory sensations via a direct electrical stimulation of the hearing nerve. They replace the function of the inner hair cells that have the role of biological microphone. Hereby, a technical simulation of the natural hearing process is performed with tonotopic presentation of the frequencies along the basilar membrane on different parts of the hearing nerve. In comparison to the natural hearing process, only a low number of electrically separated channels is available for signal transmission. This bottleneck of the electrode-nerve interface becomes especially obvious when listening to music or understanding speech in noise.

The cochlear implant systems of today are generally conceived as two component systems. The external speech processor is used for sound recording, sound preprocessing, and transformation of the acoustic information into a logical sequence of electrical impulses (so called speech processing) and it is the sender of the FM signal for a transcutaneous transmission and power supply of the implant per induction by a sending coil. The implant that is located under the skin, contains the receiver coil for reception of the FM signal, a demodulator for extraction of the electrical pulses, an electrode carrier with different intracochlear electrode contacts for transmission of the electrical impulses to the hearing nerve and telemetric measurement systems. Current cochlear implant systems dispose of a broad spectrum of signal pre-processing including directional microphones, beam former, noise elimination, and acoustic scene analysis, and of a mostly wireless interaural connection of the systems in cases of bilateral and bimodal treatment. In this way, both speech processors can be synchronized. Telemetric measurement systems record electrophysiological data with the implant itself such as electrode impedances, measurement of acoustically and electrically evoked potentials. Some systems may assess the intracochlear components of electrocochleography with Cochlear Microphonics, compound action potential of the hearing nerve and summation potential. Additionally, electrically triggered stapedius reflexes can be measured. Those objective measurements allow the intra and postoperative functional control of the implants and provide support for adjustment, which is a great advantage in children. They also allow an indirect control of the position of the implant electrodes. Different electrode systems are available for the individual cochlear implantation. Generally, a sufficient cochlear coverage should be achieved in order to stimulate possibly all spiral ganglia cells. For this purpose, insertion depths of 360° and more are needed. Some manufacturers postulate a higher cochlear coverage to reach apical neuronal elements. For cochlear implant surgery with hearing preservation, specially designed thin electrodes are used that are most frequently placed on the lateral wall and advanced depending on the hearing loss. To achieve a possibly selective stimulation with low stimulation current, preformed, perimodiolar electrodes are inserted, but generally it is less probable to preserve the hearing ability. Special electrodes are available for malformations and for ossified cochleas (double or split array. Those arrays distribute the electrode contacts on 2 electrode carriers that are inserted into the first and second turns via 2 cochleostomies. Compressed arrays are shortened electrode carriers with a normal number of stimulus contacts that are placed into the drilled initial part of the basal turn. Both procedures aim at approaching the number of intracochlear stimulus contacts as near as possible to the normal cochlear anatomy.

To achieve a secure watertight closure of the cochlea in cases of malformations, special electrodes with thickened basal end are applied.

THE CI SURGERY

As with many surgical procedures, different surgeons employ different techniques and hold different opinions related to cochlear implant surgery. However, there are some basic principles that underlie all cochlear implant surgical procedures. The major goals are: (1) to insert the electrode array as atraumatically as possible into the scala tympani, (2) to place the device on the side of the head in a manner that most protects it from trauma and (3) to ensure that the device and electrode array are secure enough to prevent movement. The intent is to accomplish these goals without damaging the surrounding tissue, device, and electrode array or causing infection and with an acceptable cosmetic result. Modifications in surgical technique often are determined by the physical and structural properties of a given device. Although the surgical technique is basically the same for both children and adults, some modifications may be required due to head size; no increased surgical risks or complications have been found in very young children (12 months). Alterations and/or adjustments to the surgical technique also may be required for special cases such as a Mondini deformity (malformed cochlea) or a hearing loss secondary to meningitis accompanied by ossification. Depending on the amount of ossification, the surgeon has choices of technique to maximize the possibility of obtaining a full insertion of the electrode array or of using a specially designed electrode array for the more heavily ossified cochleas [42]. Cochlear implant surgery is performed under general anesthesia, and typically lasts between one and four hours. Because of the immaturity of the organs, the implantation should be performed generally from the 12th month of age in cases of congenital deafness. Only in cases of particular urgency such as the risk of obliteration in the context of labyrinthitis, the implantation should be performed earlier. The implantation should include both sides to allow the development of binaural hearing with the ability of directional hearing and improved speech understanding in noise. Hereby, the simultaneous implantation should be preferred if it is possible from an anesthesiologic point of view. Compared to sequential implantation, the following advantages should be mentioned: only one hospital stay; only one anesthesia for surgery; simultaneous activation of the hearing system for the development of binaural hearing. The disadvantage is the prolonged anesthesia and the duration of surgery with the associated risk for example of increased blood loss. If sequential bilateral cochlear implantation is performed, the interval should be rather short in order to keep the auditive deprivation of the second ear as low as possible and thus to achieve a similar hearing ability for both ears. If the intervals are longer, poorer hearing results in the later implanted ear and poorer bilateral and binaural hearing performance are observed [43].

Standard Surgical Technique

The surgical technique is largely standardized and may be applied in all age groups and special cases. Generally a transmastoid surgical approach with posterior tympanostomy is performed comprising the following steps [44]:

- Retroauricular incision
- Creation of a periosteal pouch in occipital direction to insert the receiving part of the implant
- Partial mastoidectomy with exposure of the posterior wall of the auditory canal, the antrum with the incus, the mastoid course of the facial nerve, and the canal of the chorda tympani, the labyrinthine block with the 3 semicircular canals, the sigmoid sinus, and the cortex to the middle and posterior cranial fossa as well as the sinus-dura angle
- Creation of a bone bed to insert the implant at 1 cm behind and above the sinus-dura angle. Hereby, advancing sometimes onto the dura is necessary, especially in very young children. Afterwards careful coagulation is performed
- Creation of a connecting canal or tunnel to the mastoid in projection on the sinus-dura angle to securely insert and fix the electrode
- Performance of the posterior tympanostomy by removal of the bone between the bone-covered facial nerve and the chorda tympani, in order to visualize the middle ear and the relevant structures of the inner ear. Those are the promontory, the round and oval windows with stapes and stapedius tendon. In children, revisions, and malformations generally intraoperative monitoring of the facial nerve should be performed to avoid neural damages and facilitate identification of the nerve
- Opening of the cochlea by incision of the round window membrane or cochleostomy
- Insertion of the electrode carrier. Generally this should be performed in an atraumatic and slow procedure. The selected insertion depths depend on the size of the cochlea as well as the dimension of residual hearing. The insertion is performed down to the calculated depth. Depending on the electrode type, different insertion techniques, possibly using special instruments, are required. Lateral wall electrodes may be easily inserted by means of a specially developed insertion forceps in one-hand technique. Preformed electrodes require special insertion techniques. In the context of advanced-off stylet technique, the electrode is advanced into the cochlea by the stylet after partial insertion.
- Closure of the cochlea: to avoid perilymph fistula, a secure closure of the cochlea is essential. Either a fascia collar may be used that had been created before insertion, or muscle pieces that are positioned carefully around the electrode opening
- Positioning of the electrode carrier. The electrode carrier has to be securely positioned in the mastoid in order to avoid the contact with the covering skin. Although there is no absolute indication in children, in some cases a fixation of the receiver-stimulator is indicated.
- Intraoperative electrophysiology is obligatory for the intraoperative functional control of the implant as well as for measuring the stimulus response of the nerve. Via an attached coil system the implant can be activated. Then the following measurements can be performed: electrode impedances; electrically triggered stapedius reflex with determination of the threshold; electrically triggered compound

action potential of the hearing nerve (NRT, neural response telemetry); cochlear monitoring. During insertion of the electrode, residual hearing can be monitored by measuring cochlear microphone potentials outside and inside the cochlea. Critical changes of the Cochlear Microphonics amplitude indicate an impairment of the inner ear function. By repositioning the electrode, a permanent hearing loss might be avoided [45].

- Appropriate wound closure in several layers to securely cover the implant.
- The intraoperative control of the electrode position by radiography or cone beam tomography is the standard in order to identify insertion failures in time and to correct them in the same session. Furthermore, the insertion depth has to be critically verified and to be corrected, if necessary. Radiography provides important information for the postoperative fitting [46]. The chosen surgical technique is associated with a very low complication rate.
- Compressive dressing

CI COMPLICATIONS

Device Failure (Technical Complications)

Device failure occurs in about 2–4% of the cases. In children they are more frequently observed than in adults which is mainly due to a higher incidence of external forces. The continuous technical improvement of the implant, in particular since the introduction of titanium cases by nearly all manufacturers, a clear reduction of the cumulative failure rate (percentage of all implant defects over a defined observation time) could be achieved. Beside complete, also partial technical failures may occur, as for example the breakdown of an electrode contact. Re-implantation is indicated when the hearing performance is significantly impaired. Intermitting failures are difficult to assess technically as well as soft failure, i.e., the patient reports convincingly about hearing deterioration but a defect cannot be verified with the available technical means. When a device failure is observed and confirmed, re-implantation should be performed as soon as possible. This is especially true for children with implant in only one ear [47].

Medical Complications

Although the rate of complications associated with cochlear implant surgery is very small and thus postimplant complications are rare, there are certain risks involved in both the surgical procedure and postoperative period.

- Intraoperative complications – Intraoperative complications mainly occur as damage of the facial nerve, the sigmoid sinus, the internal carotid artery, or the ossicular chain. Further complications are injuries of the external wall of the auditory canal, the tympanic membrane, and the dura. The risk of facial nerve damage is somewhat

greater in those individuals with anatomic malformation of the inner ear such as are found with a Mondini deformity. In general, they can be avoided by an adequate surgical technique. A low complication rate reflects a high quality standard of cochlear implantation and sufficient training due an adequate minimum number of surgeries performed per year [48, 49].

- Postoperative complications – The difference is made between severe and mild complications. In general, those are either acute complications such as infections, postoperative bleedings, vertigo, or inner ear damage in the context of cochlear implantation with hearing preservation. In cases of late complications, usually long-term complications are observed. Those are among others the migration of the implant or the electrode when they are insufficiently fixed, e.g., without bone bed or without fixation of the electrode, thinning out of the skin covering the implant sometimes with perforation of the skin and infection, irritation of the facial nerve in the context of advanced ossification, obliteration of the cochlea in the context of labyrinthitis, or meningitis occurring after implantation [50]. Mild complications can mostly be treated conservatively. Those are also hearing deterioration with increased impedance and increased stimulus threshold, e.g., as consequence of labyrinthitis. Interestingly, those changes may also be observed in the context of overstimulation of the hearing nerve, e.g., with a very short pulse width and high rate of stimuli sequences. Hereby, the interruption of stimulation, the administration of corticosteroids as well as a careful reactivation of the stimulation are usually suitable measures to restore the stimulation capacity. Severe complications require surgical revision, for example for re-fixation of the implant and the electrode, dislocation of the implant in cases of skin defect and according plastic measures in the sense of e.g., local rotation of the temporal muscle. Meningitis is a rare though potentially serious complication in those people with inner ear deformities. Leakage of cerebrospinal fluid into the ear should be controlled if and when it occurs in order to prevent the onset of meningitis. The vestibular portion of the ear, which controls the balance mechanism, may have remaining function even when there is little or no residual hearing. When this occurs, opening the inner ear to the electrode could cause a temporary imbalance. For meningitis prophylaxis, vaccination against Pneumococci and Haemophilus influenza is recommended since CI users have an increased risk. In children, specific risks must be considered that may have severe consequences. Complications require an adequate management that must be controlled by the cochlear implant surgeon. Continuous improvement of the surgical technique led to a relevant reduction of the complication rates. With 6.9%, the percentage of inflammatory complications is clearly higher than in adults as well as the rate of electrode migration, which occurs in particular in atraumatic lateral wall electrodes. It becomes obvious by hearing loss as well as missing NRT responses to the electrode contacts that have left the cochlea. In general, surgical revision with re-insertion of the electrode and adequate fixation is required.

SETTING THE COCHLEAR IMPLANT SPEECH PROCESSOR

Approximately three to five weeks following surgery, recipients return to the cochlear implant center to receive their external equipment and to have their speech processor programmed. Device programming involves selecting and individually fitting the speech processing strategy or strategies the patient will use. Processing strategies are used to translate incoming acoustic stimuli into electrical pulses that stimulate auditory nerve fibers. Despite the numerous speech encoding strategies implemented in the various cochlear prostheses, the basic parameters of programming are neither device nor strategy dependent: the audiologist needs to obtain basic psychophysical measures i.e., thresholds and comfort levels on all electrodes. Although the basic parameters are the same, the techniques used to obtain these measures do depend on individual characteristics such as age, cognitive skills, length of deafness, and other potential factors affecting responses the use of both subjective and objective techniques. If the recipient is an adult or an older child, the subjective method can be used to set the threshold at the lowest level where the patient responds 100% of the time. The implant users also can report the level at which the loudness of the stimuli is most comfortable. After the thresholds and comfort levels are obtained for all electrodes, the computer simulates this information and translates it into an operating program that is transferred to the speech processor; live voice stimulation then can begin. Many parameters, including global increases in loudness, frequency allocation to electrodes, and speed of transmission to name a few, can be manipulated to improve the quality of sound and increase open-set speech understanding for a given patient. The precise characteristics that can be regulated are dependent on the speech processing strategy used and the manifestation of that strategy in a given cochlear implant system. Whether the patient is a child or an adult, accurate electrical thresholds and comfort levels are critical contributors to postoperative performance. Because of this, it is essential that a comprehensive schedule of programming sessions be established. The number of visits required to adequately program and maintain the speech processor depends on a number of factors including but not limited to patient age, previous auditory experience, and ability to actively participate in the device programming tasks. Furthermore, because responses to auditory stimulation from a cochlear implant can change over time, long-term audiological follow-up is required. It is recommended that cochlear implant recipients contact their cochlear implant center for speech processor programming if they or their family notices a decrease in auditory responsiveness, perception, discrimination, speech production, or a change in vocal quality in between regularly scheduled audiological appointments.

Postoperative Fitting and Hearing-Speech Training

In adults and older children, the fitting is performed psycho-acoustically with assessment of the co-called T and C levels (threshold and current of comfortable loudness) for every single electrode contact. Then the loudness between the contacts is balanced, the dynamic range is defined, and the speech processing strategy is selected. The strategy is an algorithm according to which the acoustic signal is transformed – completely or partially – into a defined sequence of electrical pulses that are then transmitted to the hearing nerve via the

electrode. The aim is a possibly physiological activation pattern of the hearing nerve. The single electrode contacts are allotted to different frequency ranges in the form of frequency bands. The allocation is made according to the subjective hearing impression and should follow the tonotopic order, i.e., high frequencies should be transmitted to the basal electrodes, low frequencies to the apical electrode contacts. An anatomically correct depiction is generally not possible because the presented frequencies and the position of the electrode contact are usually not congruent with the physiological representation on the cochlea (so called Greenwood function). In an intraoperative process, an optimized fitting may be achieved until the patient reaches an open speech understanding. After longer intervals of hearing habituation, further optimizations may follow. Already during fitting, a hearing and speech training take place. First, the focus is placed on the recognition of basic auditive categories such as loud, quiet/soft, high, low, the recognition of single syllables, of vowels and consonants, later it is speech understanding [51]. In children, fitting is performed based on objectively assessed parameters. So called NRT based maps allow an approximation of the profile over the complete electrode carrier as soon as a T and C level can be psycho-acoustically determined on an electrode contact. Additionally, electrically evoked brainstem potentials and EEG signals are applied [52]. In order to control the usage by means of a so-called datalogging, the implant registers several parameters such as the daily time of usage. This information can be used to support rehabilitation [53]. It is imperative that audiologists involved in device programming take the training courses offered by individual device manufacturers and avail themselves of the support personnel at each company in order to provide the highest quality care to the patient. Because cochlear implant speech processor technology and speech programming software constantly evolve, continuing education is a necessity.

The Use of Objective Measures in Speech Processor Programming

Over the course of the past decade there has been a trend toward implanting children at progressively younger ages. Programming the speech processor of the cochlear implant can be challenging if the recipient is either very young or has limited response capabilities. In such cases, programming techniques that are less dependent on the ability of the child to give a behavioral response can prove helpful. While there are several different types of electrically evoked potentials that could be used to assist with device programming, most of the attention in the literature has focused on the electrically evoked auditory brainstem response (EABR), the electrically evoked compound action potential (ECAP) and the electrically evoked acoustic reflex threshold (EART). All three measures have acoustic analogs, have been well studied and can be recorded in young children. When cochlear implant recipients can actively participate in the speech processor programming process, these techniques typically will not result in speech processor programs that are superior to those constructed using traditional behavioral programming techniques. Additionally, few clinics will use these tools routinely. They are typically incorporated into clinical practice in cases where the audiologist has reason to question the validity of the behavioral measures that were obtained. However, with the decrease in age of implantation and the increase in our understanding about how these tools can be used in the clinical management of cochlear implant recipients, the need for

supplemental, non-behaviorally based measures of sensitivity to electrical stimulation increasingly has become evident.

Electrically Evoked Auditory Brainstem Response (EABR)

The EABR is a recording of the synchronous neural activity in the brainstem that results when the auditory nerve is stimulated. It is recorded using commercial evoked potential equipment and surface recording electrodes positioned on the head. The EABR can be recorded either in the operating room at the time of surgery or during the postoperative period. However, obtaining a successful recording does require a very quiet or sleeping subject. The stimulus used to evoke the EABR is a biphasic current pulse that is generated by the software used to program the speech processor. Studies have shown that the EABR can be successfully measured using a variety of different implant types both in congenitally deaf children and postlingually deafened adults [54-59]. The EABR is similar in form to the acoustically evoked ABR [60] and EABR thresholds have been shown to correlate well with behavioral thresholds for the electrical stimulus used to elicit the EABR [54, 61, 62]. From a clinical perspective, however, the comparison of interest is between EABR thresholds and the levels needed to program the speech processor of the cochlear implant. Research has shown that this correlation is significant but not strong [54, 62, 63]. In general, EABR thresholds are recorded at levels where the stimulus used to program the speech processor is audible but below the maximum level of stimulation that is comfortable for a congenitally deaf child [54, 62]. This information can be useful in cases where the child is showing little or no reaction to electrical stimulation at the initial device stimulation and there is question about whether or not he/she hears the programming stimulus. The EABR threshold can provide a point to begin conditioning the child to respond to electrical stimulation. EABR thresholds tend to be relatively stable over time [64], and therefore this response provides a baseline measure of neural responsiveness to electrical stimulation that can be valuable if problems develop at any point following the initial device programming session, or hookup [65]. Additionally, in children with extremely limited response capabilities, the EABR can allow the audiologist to approximate the levels needed to program the speech processor. Few clinics routinely record the EABR. The primary reason for this is that recording this particular response requires that the subject be sedated or very still during the recording period and the process of establishing threshold on an individual electrode is time consuming. Additionally, in most cases, the relationship between the EABR threshold and the levels used to program the speech processor are not strong enough to warrant routine postoperative sedation. Some clinics do record the EABR in the operating room at the end of the surgical procedure to implant the device. Unfortunately, time is very limited during surgery and there are data suggesting that the threshold measures made in the OR immediately following insertion may change during the immediate postoperative period [54]. Nevertheless, the presence of an EABR indicates that the device and the auditory nerve are functioning. It is also possible to identify electrodes that activate the facial nerve. Because facial nerve stimulation can complicate the process of device setting, it can be very helpful to identify electrodes that cause this prior to the initial stimulation of the device. Furthermore, the parents of the child and the surgeon often find intraoperative EABR results reassuring given the necessary delay between surgery and hookup.

Electrically Evoked Compound Action Potential (ECAP)

An alternative auditory evoked potential that can be used in much the same way as the EABR is the electrically evoked compound action potential (ECAP). This is a measure of the synchronized response of the auditory nerve to electrical stimulation. Rather than being measured using surface electrodes like those used to record the EABR, the ECAP typically is recorded from an intracochlear electrode. This requires specialized technology. Cochlear Corporation was the first company to develop this technology. Since the introduction of the Nucleus CI24M device in 1998, it has been possible to measure electrically evoked intracochlear potentials in all Nucleus cochlear implant users. Cochlear Corporation refers to the software and hardware used to record this response as Neural Response Telemetry (NRT). Recently the other manufacturers have also introduced a cochlear implant with neural telemetry capabilities and is in the process of developing software to drive this system. The ECAP has several advantages over the EABR as a tool for assessing the response of the auditory system to electrical stimulation. The fact that the recording electrode is within the cochlea is advantageous for several reasons. First, it is located close to the auditory nerve, which means that the response has a large amplitude (much larger than the EABR). Second, the intracochlear location of the recording electrode results in a recording that is not adversely affected by muscle artifact, which in turn means that sedation is not necessary. This is a distinct advantage for pediatric applications. The lack of contamination by muscle artifact means that we have an electrophysiologic tool that can be incorporated into the routine post-operative evaluation of an implanted child, rather than being limited to the pre- or intraoperative period. While using an intracochlear electrode to record the ECAP is advantageous in several ways, it also can present some challenges. The primary challenge is that the close proximity of the stimulating and recording electrodes leads to significant levels of electrical stimulus artifact in the recordings. Early publications describing ECAP recordings dealt primarily with the pragmatics involved with obtaining artifact free responses [66-69]. Current research focus has shifted to studies designed to assess the response of the auditory nerve to electrical stimulation and to identify potential clinical applications for this technology [70-75]. One such application for this technology is to assist with the prediction of threshold and maximum comfort levels needed to program the speech processor of the cochlear implant. It has been shown that ECAP thresholds correlate well with behavioral thresholds if the same stimulus is used to evoke both responses [66]. Unfortunately, however, the stimulus that results in an optimal ECAP response is a relatively slow rate pulse train (≤ 80 Hz) while the stimulus used to program the speech processor of the cochlear implant is a considerably higher rate pulse train (≥ 250 Hz). Peripheral neural responses such as the ECAP (or the EABR) will exhibit adaptation effects and decrease in amplitude as the rate of stimulation is increased. Perceptually, however, the loudness of a stimulus will increase as the stimulation rate increases. This is due to the fact that the brain is able to integrate neural information over time. It is not surprising, therefore, that ECAP thresholds for an 80 Hz pulse train will exceed behavioral thresholds for the high rate stimulus used to program the speech processor of the cochlear implant. Additionally, temporal integration can vary across individuals [55]. As a result, the correlation between the evoked potential thresholds and behavioral thresholds used for programming may be expected to weaken as the difference in rate between the two stimuli increases. Like the EABR, research has shown that the ECAP is typically recorded at levels where the programming stimulus is audible to the child [70-75].

Thus, one method of using this technology with very young children is to slowly increase the programming stimulus to the ECAP threshold and begin working on conditioning the child to respond at that level. Additionally, ECAP thresholds can be used to cross check the results of behavioral testing. Very young children may let the stimulus become elevated before responding. ECAP thresholds should not be recorded at levels where the programming stimulus is inaudible. If this occurs, the behavioral thresholds should be rechecked and/or decreased to a level that is just less than the ECAP threshold. Systematic studies comparing ECAP threshold and programming levels have been published only for recipients of the Nucleus cochlear implant. Generally, these studies show correlations between NRT thresholds and the behavioral levels needed to program the speech processor of the cochlear implant that are significant, but only moderately strong [70-73]. For some people, ECAP thresholds can be recorded near the threshold for the stimulus used to program the speech processor. For other people, the electrophysiologic response is only measurable at levels that exceed maximum comfort levels for the stimulus used to program the speech processor. It is possible to use ECAP thresholds recorded on electrodes spaced across the electrode array to get an idea of how the behavioral threshold and maximum comfort levels vary across while recording electrode array. Furthermore, methods for improving the clinical utility of the NRT measures by combining the physiologic data with a limited amount of behavioral data have been proposed [69, 72]. The adequacy of programs constructed using the ECAP data was tested in a small group of Nucleus CI24M cochlear implant users [76]. Speech recognition was measured using sentences in noise for a small group of postlingually deafened adults. Performance using a program that was constructed using traditional behavioral programming techniques was contrasted with programs created based on the ECAP threshold data. The results of this study revealed that on average, individuals tended to perform slightly worse with ECAP-based programs than with programs created using standard behavioral programming techniques but this trend was not statistically significant [76]. If these results can be extrapolated to congenitally deaf children, they suggest that NRT-based speech processor programs, although not ideal, may be adequate to support speech and language development—at least until the child is older and able to be tested more accurately using behavioral techniques. These data should be reassuring to the families of children with developmental delays, who may never be able to be programmed using behavioral techniques. Additionally, future research also may demonstrate how these physiologic measures of the response of the auditory nerve to electrical stimulation may be helpful in selecting the most appropriate programming strategy for a particular cochlear implant recipient or in determining the number of electrodes to use to avoid channel interaction.

Electrically Evoked Acoustic Reflex Threshold (EART)

An alternative “objective” measure that has shown promise for assisting with device programming is the electrically evoked reflex threshold (EART). In children or adults with normal middle ear function, it is possible to elicit a reflexive contraction of the muscles of the middle ear in response to the presentation of a loud sound. Stimulation of one ear, either electrically or acoustically, causes the simultaneous contraction of the middle ear muscles in both ears. Contraction of the middle ear muscles in turn results in stiffening of the eardrum that can be measured using instrumentation available in most audiology clinics. One

advantage that the EART has over the ECAP or the EABR is that it can be elicited using the same high-rate stimulus used to program the speech processor. Additionally, recording this response does not require sedation (although it does require that the patient remain still for the time required to perform the test). These facts make the EART an ideal tool for clinical use. Several studies have explored potential clinical applications for the EART [77-81]. Many of these studies have shown relatively good agreement between the EART and the maximum comfort levels used to program the speech processor; however, to date most of the comparisons that have been published have used congenitally deaf adults who wore relatively low rate processors. Additionally, these studies report that they were unable to measure the EART for approximately 20–30% of the individuals tested [77]. This may be due either to middle ear or tympanic membrane abnormalities, inability to maintain a seal for the period of time required for testing or unusually low loudness discomfort levels. From a theoretical perspective, limiting the electrical dynamic range based on the level at which a reflex is elicited does make some sense. Congenitally deaf children often have little concept of loudness and can have unusually wide dynamic ranges. In these cases, limiting the upper levels of stimulation provided by the implant to levels that do not evoke an acoustic reflex may make the speech processor program more comfortable for the child. In children who are not responding behaviorally to electrical stimulation, stimulation levels that evoke an acoustic reflex also could be interpreted as evidence that the device is functioning and the auditory nerve is intact. Additionally, levels that evoke an EART are levels that should be audible for the child and so this may also be used for conditioning during the first stimulation settings. Hodges [77] reported that speech processor programs constructed using EART thresholds to set maximum stimulation levels are tolerated well by both children and adults. More research is needed to determine how EART measures correlate with behavioral levels used to program the speech processor of the cochlear implant for congenitally deaf children and for persons who use high rate processing strategies and to assess more fully the quality of programs created using the EART.

RESULTS

Cochlear implantation in children with congenital or prelingual deafness may have a profound impact on all aspects of communication, and the assessment battery employed for children should be broad enough to reflect these changes [82]. Thus, clinical researchers must have available a wide array of age-appropriate outcome measures that allows them to target different aspects of communication development [83]. The outcome is assessed and documented by means of standardized test procedures. The thresholds with cochlear implant are measured. They should amount to values between 20 dB and 30 dB over the whole frequency spectrum. The consistent amplification over all electrode contacts is important for a good hearing result. For the assessment of speech understanding, age-dependent test procedures are available. They register the speech understanding for numbers and monosyllables as well as the understanding of sentences in quiet and in defined noise. In the context of children, speech development is documented. In order to take into account that the test results depend on the age and to perform comparative evaluations, the scale of the CAPs (categories of auditory performance) was developed [84]. These CAPs describe the hearing

performance and its use for communication. The categories range from 0 to 9 and reach from “no auditory sensation” up to “open speech understanding” and “use of the telephone.” The majority of children with current cochlear implant devices achieve good levels of open-set word recognition [85-87]. Recognition of isolated words is a very difficult task in that there are no linguistic or contextual cues to aid the listener. When linguistic cues are available, such as in sentence recognition tasks, average performance levels are substantially higher [86]. One of the most consistent findings is that the speech perception abilities of children with cochlear implants improve with increased device experience [88]. The average spoken language processing skills of children with cochlear implants do not plateau over five or more years of device use [87]. This is in contrast to postlingually deafened adults with cochlear implants whose word recognition skills typically plateau within the first few months of device use. Children must use the sound they receive via a cochlear implant to acquire a spoken language. The development rate of children's auditory skills following implantation seems to be increasing as cochlear implant technology improves and as children are implanted at a younger age [89]. The total hearing situation in cases of bimodal and bilateral cochlear implantation can be assessed by free-field testing. Often the patients are either bimodally treated (cochlear implant and hearing aid) or bilaterally (2 cochlear implants) or have a hybrid system for electroacoustic hearing in one ear and a hearing aid in the contralateral ear (so-called combined mode). The various hearing situations have to be assessed separately and the percentage of the different hearing modalities (acoustic, electric, electroacoustic) regarding the total hearing situation must be evaluated. Numerous studies have confirmed that the successful development of language in children with early-onset deafness is strongly correlated with cochlear implantation between 12 and 24 months of age [90]. These findings reflect the importance of minimizing the interval between the onset of bilateral deafness and cochlear implantation, given that auditory development can proceed before the onset of acquired deafness and that the central auditory system is known to undergo reorganization during the period of bilateral auditory deprivation [91]. To further minimize this interval, implantation in infants with early-onset or congenital deafness before 12 months of age has been performed with good results [92, 93]. Implantation in babies as young as 3 months of age has been reported [94]; however, the reliability of the audiometric results at this early stage of development remains questionable, and surgical safety must be viewed in the context of the uncertain, theoretical, physiological advantage [95]. Moreover, there is a risk that unrecognized developmental delays will emerge with age. Nonetheless, interest in early implantation is increasing. Additional input through bilateral cochlear implants provides further benefits for adults who had bilateral hearing before their deafness; these benefits include improved hearing in noisy situations and sound localization with the use of intensity cues [96]. Relatively little has been reported regarding the outcomes of bilateral implantation in children with congenital deafness, although early data indicate better hearing in noisy situations with two implants rather than one [97, 98] an ability to discriminate between sounds at different locations [99] and electrophysiological evidence of binaural processing in the brainstem [100]. Just as the interval between the onset of bilateral deafness and cochlear implantation has implications for the development of oral speech and language, the interval between the implantation in the first and the second ear may affect the development of binaural processing in children [100]; thus, there may be at least two sensitive periods in auditory development. Risks are taken twice for bilateral implantation, with an additional theoretical risk of vestibular or balance dysfunction, or both [101,102]. Bilateral implantation

is also associated with a substantially increased cost, since two devices must be purchased and, when not done simultaneously, two procedures must be performed. However, simultaneous bilateral implantation requires less than double the surgical time and eliminates the need for two separate anesthetics, recoveries, and device activations. It may be possible to promote binaural hearing by adding a hearing aid in the ear without the implant, provided that there is sufficient residual hearing. This “bimodal” hearing can successfully supply bilateral auditory cues and access to fine-frequency information that is lost by the constant (and comparatively slow) rate of electrical pulse presentation from the cochlear implant. The decision by the FDA to approve cochlear implants for children in 1990 aroused controversy in the deaf community, with some persons asserting that deaf persons should be considered to be members of a distinct culture rather than patients with a disability, and arguing that parental approval of implants in their children is unethical [103]. More recently, however, this view has undergone some evolution. In 2000, a position paper of the National Association of the Deaf [104] stated that “cochlear implantation is a technology that represents a tool to be used in some forms of communication, and not a cure for deafness.” The paper added that “the NAD recognizes the rights of parents to make informed choices for their deaf and hard of hearing children.” Usually, early implanted children (1st year of life) achieve very good speech development scores that nearly correspond to those of normally hearing children, especially in quiet environments. In noise, however, poorer scores are observed, which reveals that a cochlear implant does not make a child normally hearing but that it is hearing impaired. Under the aspect of the overall development, it can be summarized that, compared to normally hearing people, deficits remain even in cases of early implantation that impair the cognitive development of the brain. This is mainly due to the close interrelation between the hearing system and other brain areas and functions [28]. In cases of early implantations, about 2/3 of the children may visit regular schools [105]. The professional education is usually also significantly facilitated by cochlear implant. All professions are thus open for implanted children. Usually, however, lower school categories and professional qualifications are observed [51].

Comparison of Sensory Aids in Children

In children, postimplant improvements in communication abilities may result from implant use, from maturation, or from their combined effects. The use of a within-subject design to assess cochlear implant performance does not permit researchers to separate the effects of maturation and cochlear implant use. Osberger and her colleagues were among the first to address this problem [106]. They compared the communication abilities of children with cochlear implants to those of age-matched children with similar hearing thresholds who used other sensory aids, such as hearing aids or vibrotactile aids and demonstrated that the cochlear implant users generally yielded superior results [107]. Similar studies have been carried out by other investigators to examine the effects of pediatric implantation on speech perception, speech production, or the development of language skills in children with prelingual deafness [85, 108]. Although the audiological characteristics of the control groups in these studies evolved over time as persons with more residual hearing were implanted, the vast majority of hearing aid users in these studies were profoundly deaf. Overall, these studies demonstrated that the speech perception abilities of pediatric cochlear implant recipients meet

or exceed those of their peers with unaided pure tone average thresholds ≥ 90 dB HL who use hearing aids [109].

Bilateral Implantation

In normal hearing situations, sound reaching one ear differs from sound reaching the opposite ear in two ways: there is a difference in intensity (loudness) and a difference between the times when the sound reaches each ear. These differences allow the listener to identify the direction from which a sound (and speech) emanates and to separate the speech signal from any background noise. Both of these are critical in professional and social situations because the lack of ability to understand speech in the presence of competing noise reduces an individual's ability to communicate effectively. Traditionally, cochlear implant surgery routinely has been performed in one ear due to the possible loss of residual hearing following cochlear implantation, the belief that one ear should be preserved in order to benefit from future technologies and the cost/benefit issues associated with a second device. However, because of the success of unilateral implantation and the improved functioning of individuals using binaural hearing aids, investigators have demonstrated that bilateral cochlear implantation provide increased speech understanding and localization benefits to cochlear implant users. Compared with unilaterally implanted individuals, bilateral implant recipients show better speech comprehension in noisy conditions, better directional hearing and improvement with regard to binaural mechanisms such as the head shadow and squelch effects, and better binaural summation [110-113]. Children and adolescents who underwent sequential bilateral cochlear implantation show poorer speech comprehension outcomes for the second-implanted ear than for the first side [114, 34] although these children also benefit in terms of binaural listening. In children with unilateral CIs, a modifying influence of unilateral hearing on the auditory system has been shown that induces auditory maturation; however, at an implantation age of 6.5–7.0 years, developmental maturation is less likely to be initiated [115]. Sharma et al. [116] assumed that a second, 'late' implant would stimulate cortical areas and also that there would not be normal connections either within cortical layers or to higher-order auditory and language areas, which may lead to inferior outcomes for the later-implanted ear. Nonetheless, speech recognition improves in children who undergo sequential bilateral cochlear implantation. Systematic studies on the effects of stimulation of the second-implanted ear are rare and include only limited numbers of individuals [9, 117, 118]. Unilateral cochlear implantation reorganizes the brain and generates a "stronger" and a "weaker" ear, resulting in an abnormal "aural preference" of the stronger ear [117, 119]. While this may evoke comparison with presbyopia in the visual system, the condition is significantly different in that the 'representation' of the weak ear in the cortex is preserved [119, 120]; training techniques may, therefore, provide help in overcoming the aural preference. At present, however, the easiest means of preventing abnormal auditory preference may be through simultaneously cochlear implantation or by using hearing aids to take advantage of residual hearing [34, 121]. Inter-implant interval correlates significantly with speech comprehension results obtained with the second-implanted side. To avoid abnormal aural preference in pediatric implantation, this interval should – in children first implanted under the age of 4 – be limited to less than four years. The older the children were at first implantation, the shorter the inter-implant interval needed to be. It is a direct

consequence of the inter-implant interval that children for whom this interval was longer were also older.

Cochlear Implants and Cognitive Effort

People who are hard of hearing and use hearing aids or cochlear implants often complain about being tired from straining to hear, especially in the presence of noisy environments or multiple talkers. Self-reports of listening effort and fatigue are very common even among “star” patients who score particularly well in speech recognition tests, both in quiet and in noise, yet at the cost of deploying a great deal of cognitive resources [122]. A frequent consequence of such difficulties is early exhaustion, discouragement and ultimately withdrawal from social life, where the ability to listen in challenging conditions is often required. In children and adolescents with sensorineural hearing loss, the effect of prolonged effortful listening is likely to be even more detrimental, impairing the acquisition of linguistic abilities and being an obstacle to achieving satisfactory academic performance [123]. Given these premises, it is clear that reliable measures of the listening effort experienced by hearing-impaired subjects would enable to investigate an issue of crucial importance, whose assessment is currently beyond the possibility of conventional audiometric tests. If available for clinical use, such measures could have important implications [124]: first, they would help clinicians in decision-making concerning the most appropriate treatment of hearing loss (e.g., hearing aids vs. cochlear implants); secondly, they would allow a more comprehensive assessment of functional outcomes, especially in cases where treatment is aimed at restoring binaural hearing, such as asymmetrical hearing loss or single-sided deafness [125]. Despite the growing importance of this topic, the assessment of effortful listening still represents a challenge for a number of reasons. In the first instance, there is currently no shared general definition of this concept; secondly, and subsequently, there is no agreement as to which outcome measures should be applied; thirdly, very little is known about age-related variations of the proposed outcome measures and, more specifically, about how they should be applied to pediatric subjects. In a recent consensus paper, listening effort was generally defined as “deliberate allocation of mental resources to overcome obstacles in goal pursuit when carrying out a listening task” [126], and in the frame of an established limited-capacity resource model [127]. In this model, a subject’s cognitive resources are limited; while listening, a subject deliberately allocates a part of such resources to the task, depending on the inherent demands: when demands increase, due to environmental factors (acoustically unfavorable environment), subject-related factors (e.g., hearing impairment or poor knowledge of a language) or talker-related factors (poorly intelligible accent or timbre), the amount of cognitive load invested in the task will also increase. Therefore in this paper, we will include the listening effort in the more general concept of cognitive load. In a recent paper [128], the authors applied EEG to investigate frontal theta and parietal alpha power levels of EEG in relation to cognitive load during an audiological task. In particular, the study focused on the pre-stimulus phase, i.e., the time interval when noise is on and the subject is waiting for the word to be delivered. The main findings of this research indicate that: 1) frontal theta power did not reveal a significant increase in adverse listening conditions compared to the listening-in-quiet condition; 2) parietal alpha power increased significantly in only some of the more adverse listening conditions compared to the listening-in-quiet

condition. Going back to the study hypothesis, we found that only alpha power met expectations that it would be higher in the most difficult listening conditions, whereas theta power showed no significant variations. An increase in theta power is unanimously considered as an electrophysiological marker of engagement in a task [129]. Over the years, it has been studied in relationship to cognitive load, excitement and interest, high attentional demands, task difficulty, cognitive and mental efforts [130, 131]. The finding of non-significant changes for theta power throughout the various listening configurations assessed in this research may seem contradictory to that reported in the existing literature. A possible interpretation would be to assume that the task was not exciting enough for the subjects, and a higher degree of mental effort would have been necessary to elicit significant variations in theta band. Another explanation concerning why theta power levels did not increase could be that in the present study the pre-stimulus interval (i.e., the interval before word onset) was analyzed. In this “pre-word” phase, subjects were only hearing the competing babble noise, anticipating of the test signal but not actively engaged in decoding a test sound signal. In a recent experiment on normal-hearing subjects conducted with an auditory oddball task, Wisniewski et al. [132] found no significant theta variations either before word onset or during “passive” exposure to stimuli, namely as subjects were engaged in another activity. Thus, the pre-stimulus phase of our study may be equivalent to the passive exposure described in Wisniewski's work, where subjects were asked not to pay attention to background noise, but to focus on the incoming word stimuli. However, the significant within-subject correlation found between frontal theta and parietal alpha power levels suggests that theta activity could be a potential indicator of cognitive resource deployment in effortful audiological tasks, providing a higher degree of effort is required or a different epoch (e.g., during or poststimulus) is analyzed. The main finding of the present study was the significant increase of parietal alpha power in two of the three most challenging listening conditions, i.e., binaural noise and noise delivered to the worse hearing ear. This verified the study hypothesis concerning alpha power only partially, since the expected rise in the acoustically most adverse condition, where noise was delivered to the better ear, was not observed. Such results need to be interpreted in the light of the large amount of literature investigating the general relevance of alpha activity and its possible generators, bearing in mind that only a few studies have focused specifically on the impact of various listening tasks. The earliest research investigating the behavior of parietal alpha power in the pre-stimulus phase was conducted using visual stimuli. Parieto-occipital alpha power was shown to increase as tested subjects are required to direct attention to a relevant stimulus while neglecting other task-irrelevant stimuli, such as portions of space containing distractor information [133], colors, or motions [134]. Other studies have even demonstrated that selective increases of alpha activity occur retinotopically over areas of the parietooccipital cortex where distracting visual stimuli are likely to be processed [135, 136]. Also works using a double modality of stimulus presentation (e.g., visual vs auditory) have confirmed that alpha power increases as tested subjects try to suppress one modality in favor of another one [137, 138]. When purely auditory tasks were used, alpha power in the parietal and occipital cortex was once again found to increase as subjects were preparing for expected auditory stimuli [139, 140]. A lateralization of alpha band activity was also observed, whereby alpha power increases over the parietal cortex contralateral to the to-be-ignored stimulus. Our results with the “binaural noise” and “noise to the worse ear” listening conditions seem to fit the model, suggesting that increases in the parietal alpha power can be an indicator of attentional

suppression even in a pediatric sample [128]. In that study, words were the relevant auditory stimulus and babble noise was irrelevant to the task and thus a to-be-ignored stimulus or distractor. Overall, this is consistent with recent theories attributing task-related increases of alpha activity to the activation of a supramodal functional inhibition system [141, 142], i.e., a “top-down” gating system where inhibitory neural pathways eliminate task-irrelevant stimuli and constrain potentially erroneous behaviors. To the best of our knowledge, this is the first time that a drop in alpha power has been observed in the most challenging listening condition tested (noise was delivered to the better hearing ear). As stated above, under this circumstance our study hypothesis was not fulfilled, whereby alpha power fell to the level of that observed in the quiet test condition. Possibly, this is the reason why no correlation could be found between alpha power levels and SRT scores: whereas average SRT scores decreased with increasing difficulty of the task (i.e., from Quiet to better ear), alpha power levels increased from Quiet to worse ear, but then decreased again in the better ear condition. This “alpha drop phenomenon” may be explained by subjects mentally withdrawing from the task, when it became exceeding difficult [143]. In their “Framework for Understanding Effortful Listening” model, Pichora Fuller et al. [126] postulate that listening effort increases as task demands increase as long as the subject is motivated toward the task itself, up to a point where task demands exceed the subject's cognitive resources. When this occurs, the subject loses motivation and stops deploying these resources in the task. Specifically, it is likely that the “noise to better ear condition” was too difficult for the subjects selected in the study, whose SRT in that condition was on average 15 dB, that is to say well above the ≥ 10 SNR level at which the EEG recordings took place. In this case, it is plausible that the patients stopped directing their attention selectively toward the presented words and completely lost their overall “engagement” in the task. A support to this interpretation comes from the work by Wizniewski [140], in which alpha power levels were compared in normal-hearing adults during an active listening and a passive exposure experiment: during the passive experiment, alpha power levels dropped to rest values. Thus, it is plausible that in our subjects loss of interest in a too difficult task may have equaled the “passive exposure” condition in Wizniewski's study [140]. Overall, our results suggest that EEG alpha activity derived from the parietal cortex can be used in pediatric subjects with sensorineural hearing loss as an objective measure of cognitive load during effortful listening. In particular, since the pre-stimulus phase was analyzed, sustained attention and selective inhibition seem to be the likeliest behavioral correlates of the observed alpha variations. If confirmed on larger samples, the alpha power drop characterizing the most adverse listening condition suggests that cognitive withdrawal from a task can also be measured objectively. Even if consistent with recent works in the literature, the results of our study should be interpreted with caution and be supported by further investigations in larger cohort datasets. Firstly, our data refer to a pediatric population in whom the brain is notoriously immature and, as a consequence, normative data is age dependent. Most of the literature, on the contrary, reports on adult or elderly subjects. For example, it is known that alpha frequency itself increases in a non-linear way [144], whereas global alpha and theta power increase and decrease, respectively, from childhood to puberty [145]. Secondly, the lack of normative data from normal-hearing subjects makes it impossible, at this point, to use absolute alpha and theta power levels to quantify cognitive load. However, if confirmed by further research on diverse and larger samples, these findings could be used to refine indications for hearing aid or cochlear implant

treatment of sensorineural hearing loss, and for a more in-depth assessment of the audiological outcomes of listening devices.

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Chapter 69

PRESBYASTASIS: FROM DIAGNOSIS TO MANAGEMENT

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ABSTRACT

Currently, the elderly population (> 65 years old) is in very growth. In fact, in Italy old age index (number of elderly per 100 persons under the age of 14 years) is estimated to be 157,7 and is projected to increase to 257,9 in the year 2065 [1, 2]. The increase of the elderly population determines the increase of the age-dependent diseases including also impairment of the vestibular function, this problem is defined “presbiastasia”. Patient suffering from this condition exhibit disturbances of static and dynamic postural control with far less frequent cases of relapsing objective rotatory vertigo. Occasionally, they also report a feeling of insecurity in new or unknown environments, increasing the risk of falls.

These balance disorders significantly affect patients’ private and social life, as they interfere with a large number of daily activities, as transfer into bed, ambulation, car transfers, eating, using of telephone. The number of patients with this disease is expected to increase with the rise in the number of elderly population and this has important implications on the national health system's resources. Thus, the rehabilitation of these balance disorders presents serious difficulties. This explains the great number of techniques, with or without the use of equipment, which have so far been proposed. Some authors suggested to apply actual protocols, more or less modifiable according to patient characteristics; others recommended individual exercises or special equipment-aided techniques.

In these cases, vestibular rehabilitation allows to stimulate the equilibrium system by preventing and slowing down the effects of aging, through the use of “adaptive, substitutive and custom” strategies.

Keywords: dizziness, fall, presbiastasia

INTRODUCTION

“Dizziness is prevalent in all adult populations, causing considerable morbidity and utilization of health services.

In the community, the prevalence of dizziness ranges from 1.8% in young adults to more than 30% in elderly people... Dizziness is one of the most challenging symptoms in Medicine: it is difficult to define, impossible to measure, a challenge to diagnose, and troublesome to treat. ...Not the best example of evidence based practice...” [3] the dizziness prevalence in elderly people is very high. Often the dizziness is associated with a poor state of health.

In this chapter is very important the study of global balance function, in fact we have to study vision, hearing, posture and proprioception functions in all of patients. Why? Because in particular hearing function is considered by some authors to be an indispensable element for maintaining equilibrium [4-10].

The aims of rehabilitation in elderly subject are to train them how to control their movements, to teach how to get up after a falling, to walk in harmonious way. Thus, the doctor's purpose is to establish a rehabilitative plan to follow, considering:

- the patient's age
- the cognitive state of the patient
- the social factor
- the education
- vestibular canal and/or otolithic impairment
- muscle pain
- osteo-articular development

This information is essential for the initial assessment of the patient, because this is an individual rehabilitation plan.

PATIENT'S EVALUATION

Falling is the first problem of these patients, therefore is essential to predict the risk to fall and reduce it. The principal tests used are: Tinetti balance assessment tool [11], timed “get up and go” test [12-14], Berg balance test.

TINETTI PERFORMANCE ORIENTED MOBILITY ASSESSMENT (POMA)

It is a qualitative test involving static and dynamic tasks which serves mainly to predict the risk to fall in elderly subjects.

BALANCE SECTION

Patient sitting in hard, armless chair

Sitting Balance	Leans or slides in chair = 0 Steady, safe = 1		
Rises from chair	Unable to without help = 0 Able, uses arms to help = 0 Able without use of arms = 2		
Attempts to rise	Unable to without help = 1 Able, requires > 1 attempt = 1 Able to rise, 1 attempt = 2		
Immediate standing Balance (first 5 seconds)	Unsteady (staggers, moves feet, trunk sway) = 0 Steady but uses walker or other support = 1 Steady without walker or other support = 2		
Standing balance	Unsteady = 0 Steady but wide stance and uses support = 1 Narrow stance without support = 2		
Nudged	Begins to fall = 0 Staggers, grabs, catches self = 1 Steady = 2		
Eyes closed	Unsteady = 0 Steady = 1		
Turning 360 degrees	Discontinuous steps = 0 Continuous = 1 Unsteady (grabs, staggers) = 0 Steady = 1		
Sitting down	Unsafe (misjudged distance, falls into chair) = 0 Uses arms or not a smooth motion = 1 Safe, smooth motion = 2		
	BALANCE SCORE	/16	/16

GAIT SECTION

Patient standing with therapist, walks across room (+/- aids), first at usual pace, then at rapid pace.

Indication of gait (Immediately after told to 'go'.)	Any hesitancy or multiple attempts= 0 No hesitancy= 1		
Step length and height	Step to = 0 Step through R= 1 Step through L= 1		
Foot clearance	Foot drop= 0 L foot clears floor= 1 R foot clears floor= 1		
Step symmetry	Right and left step length not equal= 0 Right and left step length appear equal= 1		
Step continuità	Stopping or discontinuity between steps= 0 Steps appear continuous = 1		
Path	Marked deviation = 1 Mild/moderate deviation or uses w. aid = 1 Straight without w. aid = 2		
Trunk	Marked sway or uses w. aid = 0 No sway but flex. knees or back or uses arms for stability = 1 No sway, flex., use of arms or w. aid = 2		
Walking time	Heels apart = 0 Heels almost touching while walking = 1		
	GAIT SCORE	/12	/12
	Balance score carried forward	/16	/16
	Total Score = Balance + Gait score	/28	/28

RISK INDICATORS

Tinetti Tool Score	Risk of Falls
≤18	High
19-23	Moderate
≥24	Low

stands up from a chair, walks 3 meters, turns around, and sits down again. The results are:

- normal mobility: patients who are autonomous for balance and for prehension tasks perform it in less than 10 seconds
- normal limits for weak, elderly and disabled people: patients who are independent for transfers only perform them in less than 20 seconds

- a range higher than 20 seconds means the person needs assistance outside and indicates the necessity of further examinations and interventions [15]
- a score of 30 seconds or more suggests that the person has an severe risk to fall

BERG'S BALANCE SCALE

Berg's Balance Scale (BBS) was developed in 1989 via health personnel and patients' interviews that studied the various methods used to assess balance. Although the Berg Balance Scale was originally developed to measure balance in the elderly people, it has been used to measure balance in a wide variety of patients [16-18]. This test graded items from 0 (bad) to 4 (good):

- Sitting position without back support nor armrests
- Going from standing to sitting position
- Going from sitting to standing position
- Transfer from one seat to another
- Standing upright with closed eyes
- Standing upright with feet together
- Standing upright with feet in tandem position (one foot behind the other along a line)
- Standing on one foot
- Trunk rotation
- Picking up an object from the floor
- Turning around completely (360°)
- Climbing up one step
- Bending forward

REHABILITATION STRATEGY

Proprioceptive training is based on stimulation of the neuromotor system. This training consists of series of exercises designed to re-educate reflexes. The goal is to achieve optimal control of posture and balance. The proprioceptive training must be set on situations that lead the subject to lose balance, in order to activate the muscles quickly and correctly. The improvement of the equilibrium happens both by the maintenance of the position and the ability to quickly correct the imbalances. To achieve the objective of a correct stimulation of proprioceptive reflexes it is necessary that the elderly subject is motivated and considered the protagonist of his own improvement. The training technique is based on controlled stress and it is applied to the joints, using both unloading and natural loading exercises, resting on the ground or on oscillating surfaces of varying difficulties, such as boards, bouncers, skymmi, bosu, trampolines and many others devices. All proprioceptive exercises must be performed avoiding wearing shoes, in order not to divert the proprioceptive sensations from the foot. To further intensify the training, you can perform the exercises with your eyes closed, as the balance is also controlled by the exteroceptors (view and vestibular apparatus),

which receive information from the outside world. Information coming from exteroceptors and proprioceptors gives the exact position of one's body.

PROPRIOCEPTIVE TRAINING

Proprioceptive exercises to restore a correct load:

- Step training with scales to re-establish a correct load during the step
- Throw a ball and keep the balance
- Build an obstacle course and cross it

Exercises with boards:

- Sitting with a foot on a board, move the ankle in flexion and extension
- Sitting with a foot on a rectangular board, move the ankle in flexion and extension
- Sitting with a foot on a rectangular board, move the ankle in flexion and extension and foot in inversion and eversion

These exercises must be repeated first in a monopodalic and then bipodalic manner. According to the characteristics of the subject (osteo-articular, muscular and cognitive conditions), these exercises must also be done in orthostatism, using boards or on a stable plane.

PROPRIOCEPTIVE SELF-ANALYSIS

The technique is based on the cortical ability to reconstruct postural attitude, relying mainly on proprioceptive inputs. The subject is placed in front of a squared mirror. In this way the patient can assume different positions. The technique consists in getting reconstructing body position, first thanks to the image reflected in the mirror, then the mirror is moved away, the patient must memorize and therefore maintain the correct position. By repeating this exercise many times the subject becomes more aware of his body. This method has many advantages: it activates central mechanisms that are rarely used in rehabilitation, patients can perform the exercises at home, and results are evident to the subject. Moreover, this method helps elderly people to accept their image and coordinate movements.

LEARNING TO GET UP AFTER A FALL

Falling does not only represent a trauma itself; it also indicates a general failure of the balancing system, in fact, "Falls are a marker of frailty, immobility, and acute and chronic health impairment in older persons. Falls in turn diminish function by causing injury, activity limitations, fear of falling, and loss of mobility" [19].

The physiotherapist gets the patient quickly to lie down on the back. The patient is shown how to swing a leg after swinging an arm to find himself lying on face down, and then to crouch to get on all limbs in order to draw near to a table or any furniture. He is then shown how to raise a knee, and to stand up progressively by lean on to the piece of furniture. Repeating the exercises helps overcome the problem of falling.

CONCLUSION

The aim of our chapter is to find a personalized rehabilitative project-program that leads the elderly people to achieve a high and autonomous lifestyle. The best tool to employ is a multidisciplinary approach starting from the diagnosis until the treatment of the various disabilities old-age related, without the mindless claim to cure an inexorable physiological process that is old age. The key of the success in achieving this result is the team work involving different professional figures like physiatrist, physiotherapist, neurologist and otolaryngologist. Within this multidisciplinary team, physiatrist plays a managing role. The treatment is based on proprioceptive rehabilitation exercises, on the reduction of auditory [20-23], visual and neurological problems. Certainly the results are always closely related to the motivational support given by the team work to the patient. Furthermore, it is essential for the patient to interact with the surrounding environment in order to overwhelm his anxiety and fear improving, in this way, his quality and length of life [24-27].

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